

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 July 2006 (13.07.2006)

PCT

(10) International Publication Number
WO 2006/074057 A2

(51) International Patent Classification: **Not classified**

(21) International Application Number:
PCT/US2005/047402

(22) International Filing Date:
28 December 2005 (28.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/640,439 30 December 2004 (30.12.2004) US
60/704,863 1 August 2005 (01.08.2005) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: KINASE MODULATORS AND METHOD OF USE

(57) Abstract: The invention provides compounds and methods for inhibition of kinases, more specifically IGF 1 R kinases. The invention also provides compounds and methods for inhibition of wildtype Abl. The invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Compounds of the invention inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, and the invention includes compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.



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Kinase Modulators and Method of Use

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial No. 60/640,439 filed December 30, 2004, and U.S. Provisional Patent Application Serial No. 60/704,863, filed August 1, 2005, both of which are incorporated by reference herein in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for modulating protein kinase enzymatic activity and the resultant modulation of cellular activities such as proliferation, differentiation, programmed cell death, migration, chemoinvasion and metabolism. Even more specifically, the invention relates to compounds which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat various disease states such as cancer, metabolic, and inflammatory diseases is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins at the hydroxy groups of tyrosine, serine and threonine residues of proteins. The kinase complement of the human genome contains 518 putative protein kinase genes (Manning et al, Science, (2002), 298, 1912). The consequences of this activity include effects on cell differentiation, proliferation, transcription, translation, metabolism, cell cycle progression, apoptosis, metabolism, cytoskeletal rearrangement and movement; *i.e.*, protein kinases mediate the majority of signal transduction in eukaryotic cells. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to cancer. Chromosomal mapping has revealed that over 200 kinases map to disease loci, including cancer, inflammatory and metabolic disease.

[0004] Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and -beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (Flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al. (1994) DN&P 7(6): 334-339, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Syk/Zap70, Fes/Fps, Fak, Jak, and Ack. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen (1993) Oncogene, 8:2025-2031, which is hereby incorporated by reference.

[0007] Serine-threonine kinases play critical roles in intracellular signal transduction and include multiple families, such as STE, CKI, AGC, CAMK, and CMGC. Important subfamilies include, the MAP kinases, p38, JNK and ERK, which modulate signal transduction resulting from such diverse stimuli as mitogenic, stress, proinflammatory and antiapoptotic pathways. Members of the MAP kinase subfamily have been targeted for therapeutic intervention, including p38a, JNK isozymes and Raf.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, such as immunological disorders, metabolic and cardiovascular diseases, inflammatory

diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0009] One therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0010] Goals for development of small molecule drugs include modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. (2001) *Drug Disc Technol* 6, 1005-1024). Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. Cell antiproliferative agents are also desirable to slow or stop the growth of tumors.

[0011] Insulin is the central hormone governing metabolism in vertebrates (reviewed in Steiner et al. (1989) in *Endocrinology*, DeGroot, eds. Philadelphia, Saunders: 1263-1289). In humans, insulin is secreted by the beta cells of the pancreas in response to elevated blood glucose levels, which normally occur following a meal. The immediate effect of insulin secretion is to induce the uptake of glucose by muscle, adipose tissue, and the liver. A longer-term effect of insulin is to increase the activity of enzymes that synthesize glycogen in the liver and triglycerides in adipose tissue. Insulin can exert other actions beyond these "classic" metabolic activities, including increasing potassium transport in muscle, promoting cellular differentiation of adipocytes, increasing renal retention of sodium, and promoting production of androgens by the ovary. Defects in the secretion and/or response to insulin are responsible for the disease diabetes mellitus, which is of enormous economic significance. Within the United States, diabetes mellitus is the fourth most common reason for physician visits by patients; it is the leading cause of end-stage renal disease, non-traumatic limb amputations, and blindness in individuals of working age (Warram et al. (1995) in "Joslin's Diabetes Mellitus", Kahn and Weir, eds., Philadelphia, Lea & Febiger, pp. 201-215; Kahn et al. (1996) *Annu. Rev. Med.* 47:509-531; Kahn (1998) *Cell* 92:593-596). Beyond its role in diabetes mellitus, the phenomenon of insulin resistance has been linked to other pathogenic disorders including obesity, ovarian hyperandrogenism, and hypertension. Insulin resistance, hyperestrinism and the associated hyperandrogenism may play a role in the onset of some

malignancies, such as endometrium cancer, breast cancer and prostate cancer (Guastamacchia E, et al. (2004) *Curr Drug Targets Immune Endocr Metabol Disord.* 4:59-66). The physiologic effects of insulin are mediated by specific association of the peptide hormone with a cell surface receptor, the insulin receptor (INRS), with concomitant activation of a signal transduction pathway in responding tissues. The INRS has been well characterized at the molecular level; it is a member of a large family of tyrosine kinase receptors (Ullrich et al. (1985) *Nature* 313:756-761). INRS signaling has been shown to involve a number of intracellular participants (White and Kahn (1994) *J. Biol. Chem.* 269:1-4; Kahn et al. (1998) *Supra.*). These participants include the so-called insulin receptor substrate, or IRS-1, which is phosphorylated by an activated insulin receptor kinase. IRS-1 in turn associates with phosphatidylinositol-3-kinase (PI3K). A number of other protein kinases and signaling proteins have been implicated in this signal transduction mechanism and presumably participate in a "kinase cascade" that leads to the modification and regulation of a host of intracellular enzymes, structural proteins, and transcription factors.

[0012] Insulin-like Growth Factor 1 Receptor (IGF1R) is an integral membrane tyrosine kinase receptor that binds insulin-like growth factor with high affinity. IGF1R plays a critical role in transformation events and human cancer (LeRoith and Helman (2004) *Cancer Cell* 5:201-202). It is highly over-expressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival through the PI3K pathway, and also the p53 pathway. IGF1R has been linked to various disease states, such as breast and ovarian cancer (Maor et al. (2000) *Molec. Genet. Metab.* 69: 130-136), metastatic uveal melanoma (All-Ericsson, C. et al. (2002) *Invest. Ophthalm. Vis. Sci.* 43: 1-8), macular degeneration (Lambooij, A. C. et al. (2003) *Invest. Ophthalm. Vis. Sci.* 44: 2192-2198), and intrauterine growth retardation and poor postnatal growth (Roback, E. W. et al. (1991) *Am. J. Med. Genet.* 38: 74-79), among others.

[0013] Microtubules have a central role in the regulation of cell shape and polarity during differentiation, chromosome partitioning at mitosis, and intracellular transport. Microtubules undergo rearrangements involving rapid transitions between stable and dynamic states during these processes. Microtubule affinity regulating kinases (MARKs) are a novel family of protein kinases that phosphorylate microtubule-associated proteins and trigger microtubule disruption (Drewes, G., et al. (1997) *Cell* 89: 297-308). EMK1 (MARK2) is a serine/threonine protein kinase with 2 isoforms, which differ by the presence or absence of a 162-bp alternative exon (Espinosa, L. and Navarro, E. (1998) *Cytogenet. Cell Genet.* 81:278-282). Both human isoforms are co-expressed in a number of cell lines and tissues, with the

highest expression found in heart, brain, placenta, skeletal muscle, and pancreas, and at lower levels in lung, liver, and kidney (Inglis, J. et al. (1993) *Mammalian Genome* 4: 401-403). EMK1 is a regulator of polarity and also a modulator of Wnt-beta-catenin signaling, indicating a link between two important developmental pathways (Sun T et al. (2001) *Nature Cell Biology* 3: 628-636). Due to the physical location of this gene, 11q12-q13, EMK1 is a candidate gene for carcinogenic events (Courseaux, A. et al. (1995) *Mammalian Genome* 6: 311-312), and has been associated with colon and prostate cancer (Moore, T. M., et al. (2000) *J Biol Chem* 275:4311-22; Navarro, E., et al. (1999) *Biochim Biophys Acta* 1450: 254-64). Increased expression of EMK1 has been associated with increased inflammation in protocol biopsies of transplanted patients (Hueso M et al. (2004) *Biochimica Et Biophysica Acta* 1689: 58-65). Emk protein kinase is also essential for maintaining immune system homeostasis and its loss may contribute to autoimmune disease in mammals (Hurov J et al. (2001) *Molecular and Cellular Biology* 21: 3206-3219).

[0014] Cell motility is stimulated by extracellular stimuli and initiated by intracellular signaling proteins that localize to sites of cell contact with the extracellular matrix termed focal contacts. Focal adhesion kinase (FAK) is an intracellular protein-tyrosine kinase (PTK) that acts to regulate the cycle of focal contact formation and disassembly required for efficient cell movement. FAK is activated by a variety of cell surface receptors and transmits signals to a range of targets. FAKs are known to target paxillin and are substrates for Src family kinases (Calalb et al. (1995) *Molec. Cell. Biol.* 15: 954-963). Thus, FAK acts as an integrator of cell motility-associated signaling events. Activation of FAK may be an important early step in cell growth and intracellular signal transduction pathways triggered in response to certain neural peptides or to cell interactions with the extracellular matrix. FAK also functions in promoting cell invasion (Schlaepfer DD and Mitra SK (2004) *Curr Opin Genet Dev.* 14: 92-101). FAK2 is another member of the FAK subfamily of protein tyrosine kinases. The FAK2 gene encodes a cytoplasmic protein tyrosine kinase involved in calcium-induced regulation of ion channels and activation of the map kinase signaling pathway. FAK2 protein may represent an important signaling intermediate between neuropeptide-activated receptors or neurotransmitters that increase calcium flux and the downstream signals that regulate neuronal activity. FAK2 undergoes rapid tyrosine phosphorylation and activation in response to increases in the intracellular calcium concentration, nicotinic acetylcholine receptor activation, membrane depolarization, or protein kinase C activation. FAK2 binds CRK-associated substrate, nephrocystin, GTPase regulator associated with FAK, and the SH2 domain of GRB2.

[0015] Abl (Abelson murine leukemia viral oncogene homolog) is a protein tyrosine kinase involved in cellular proliferation, differentiation, adhesion and survival. Alterations of Abl by chromosomal translocation lead to malignant transformations. The t(9;22) translocation, resulting in a fusion protein Bcr-Abl with constitutive kinase activity, occurs in greater than 90% of chronic myeloid leukemia (CML), 25-30% of adult and 2-10% of childhood acute lymphoblastic leukemia (ALL), and rare cases of acute myelogenous leukemia (AML). The tyrosine kinase activity of Bcr-Abl is critical for malignant transformation. Gleevec® (Imatinib mesylate), a small-molecule inhibitor of Bcr-Abl kinase, was approved for the treatment of CML in 2001. Despite its early success, patients treated with Gleevec® have developed resistance to the therapy. Various mutations in the Abl kinase domain have been identified and are responsible for Gleevec®-resistant disease progression (Gorre ME, Mohammed M, Ellwood K, et al., *Science* 2001; **293**:876-80). Molecular studies have demonstrated that these mutations modify the protein conformation of the kinase active site and thus interfere with the binding of Gleevec® (Shah NP, Nicoll JM, Nagar B, et al., *Cancer Cell* 2002; **2**:117-25; Branford, S. et al., *Blood* **99**, 3472-3475 (2002); Branford, S. et al., *Blood* **102**, 276-283 (2003); Branford, S. et al., *Blood* **104**, 2926-2932 (2004); Hochhaus, A. et al., *Leukemia* **16**, 2190-2196 (2002); Roche-Lestienne, C. et al., *Blood* **100**, 1014-1018 (2002); Roche-Lestienne, C., Lai, J. L., Darre, S., Facon, T. & Preudhomme, C., *N. Engl. J. Med.* **348**, 2265-2266 (2003)). Second-generation Gleevec® analogs (e.g. AMN107) and other kinase inhibitors (e.g. Dasatinib) have been developed to inhibit many of the Gleevec®-resistant Abl mutants (Martinelli G, Soverini S, Rosti G, Cilloni D, Baccarani M., *Haematologica* 2005; **90**:534-41). Both AMN107 and Dasatinib have shown improved response rates in CML patients, as compared to Gleevec®. However, neither compound can inhibit the T315I Abl mutant. It has been reported that a significant number of patients who relapsed in the treatment with Dasatinib have had or developed the T315I mutation (Shah NP, Sawyers CL, Kantarjian HM, et al., "Correlation of Clinical Response to BMS-354825 with BCR-ABL Mutation Status in Imatinib-Resistant Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Associated Acute Lymphoblastic Leukemia (Ph+ ALL)"; ASCO Annual Meeting 2005; Abstract #6521).

[0016] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and metabolism is an object of this invention. In addition, there is an unmet medical need to develop inhibitors

of various forms of Abl, including the T315I mutant, for the treatment of Gleevec[®]-resistant CML and Bcr-Abl positive ALL.

SUMMARY OF THE INVENTION

[0017] In one aspect, the present invention provides compounds and compositions (including pharmaceutical compositions) for modulating the activity of IGF1R and methods of treating diseases mediated by the activity of IGF1R utilizing the compounds and pharmaceutical compositions thereof.

[0018] In another aspect, the invention provides for compounds and compositions (including pharmaceutical compositions) for the inhibition of Abl mutant.

[0019] In still another aspect, the invention provides methods of screening for modulators of kinase activity. The methods comprise combining a composition of the invention and at least one candidate agent and determining the effect of the candidate agent on the kinase activity.

[0020] In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical compounds and/or compositions of the present invention, including IGF1R activity modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (*e.g.*, diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals or biological products, which instructions optionally include notice of approval by the agency.

[0021] In still yet another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

[0022] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

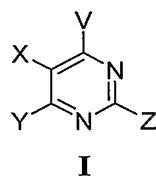
DETAILED DESCRIPTION OF THE INVENTION

[0023] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as arteriosclerosis, myocardioinfarction, ischemia,

stroke and restenosis; metabolic disorders and diseases such as diabetes, obesity and hypercholesterolemia; and other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritis, macular degeneration, diabetic retinopathy.

[0024] It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) but may still require treatment. For example, during wound healing, the cells may be proliferating “normally”, but proliferation and migration enhancement may be desired. Alternatively, reduction in “normal” cell proliferation and/or migration rate may be desired.

[0025] The present invention comprises a compound for modulating protein kinase enzymatic activity, according to Formula I,



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

V is NR_1R_{1a} , or $\text{O}-\text{R}_1$, wherein

R_1 is H, CN, halo, $-\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{NR}_{13}\text{R}_{14}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6$ alkyl- R_{20} , wherein R_{20} is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, $\text{C}_3\text{-C}_7$ heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from $\text{C}_1\text{-C}_6$ alkyl, and $-\text{C}_0\text{-C}_6$ alkyl- R_{21} ;

R_{1a} is H or $\text{C}_1\text{-C}_6$ alkyl; or

when V is NR_1R_{1a} , R_1 and R_{1a} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing, in addition to the nitrogen, up to two additional heteroatoms independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}_{13}\text{R}_{14}$ or $\text{C}_3\text{-C}_7$ cycloalkyl;

X is H, halo, $\text{C}_1\text{-C}_6$ alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O}-\text{C}_1\text{-C}_6$ alkyl, or $\text{N}(\text{R}_{13})-\text{C}(\text{O})-\text{C}_1\text{-C}_6$ alkyl;

Y is H, halo, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_6$ alkyl- $\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{O}-\text{C}_1\text{-C}_6$ alkyl, $-\text{O}-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6\text{-alkyl-}\text{R}_{21}$, $-\text{O}-\text{R}_{21}$, $-\text{C}(\text{O})-\text{R}_{21}$, $-\text{O}-(\text{CH}_2)_n-\text{R}_{21}$, $-\text{C}(\text{O})-\text{NR}_{13}\text{R}_{14}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})\text{-aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-heterocyclyl}$;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, aryl-C₁-C₆ alkyl-, aryl-(CH₂)_n-O-(CH₂)_n-aryl-, arylOH, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, or a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is NR₁₃R₁₄, N(R₁₃)C(O)-C₁-C₆ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, C(O)O-(CH₂)_n-phenyl, and C(O)-C₁-C₆ alkyl;

Z is H, NR₂R₃, -S-R_{2a}, or -O-R_{2a}, wherein

R₂ is -C₁-C₆ alkyl, -C₁-C₆ alkyl-NR₁₃R₁₄, -C(O)-aryl, -C₀-C₆-alkyl-aryl, -C₀-C₆-alkyl-heteroaryl, -C₀-C₆-alkyl-(C₃-C₇-cycloalkyl), -C₀-C₆-alkyl-heterocyclyl, or -C₀-C₆ alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein

each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, C₃-C₇ cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO₂, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, N(R₁₃)C(O)-C₁-C₆ alkyl, -SO₂NR₁₃R₁₄, -O-C(O)-NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, -O-(CH₂)_n-NR₁₅R₁₆, -C₁-C₆ alkyl-NR₁₃R₁₄, -N(R₁₃)-C(O)-C₁-C₆ alkyl, -N(R₁₃)-C(O)-aryl, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-aryl, -O-(CH₂)_n-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-C(O)-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-O-C₁-C₆ alkyl, -C₀-C₆ alkyl-N(R₁₃)-C(O)O-C₁-C₆ alkyl, -C₀-C₆alkyl-C(O)-heterocyclyl, -C₀-C₆alkyl-C(O)-heteroaryl, -C₀-C₆alkyl-C(O)-aryl, -C₀-

C₆-alkyl-R₂₁, aryloxy, -O-(CH₂)_n-R₂₁, -SO₂-heterocyclyl, N(R₁₃)-C(O)-C₃-C₇-cycloalkyl, -C₀-C₆alkyl C(O)O-R₂₁, C₃-C₇-cycloalkyl, -C₀-C₆alkylR₂₁, -SC₁-C₆alkyl or C₁-C₆ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, CF₃, C₁-C₆ alkyl, C₁-C₆ haloalkoxy, NR₁₃R₁₄ and C₁-C₆ alkoxy;

R₃ is H or C₁-C₆ alkyl;

or R₂ and R₃ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing up to three heteroatoms independently selected from O, N, and S, and wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two of halo or C₁-C₆ alkyl;

R_{2a} is aryl or C₀-C₆ alkyl-heteroaryl, wherein the aryl and heteroaryl are optionally substituted with aryl, -N(R₁₃)-C(O)-C₃-C₇ cycloalkyl or -C(O)NR₁₃R₁₄;

R₁₃ and R₁₄ are independently H or C₁-C₆ alkyl;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, or -C(O)O-C₁-C₆ alkyl;

R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

n is 0-6;

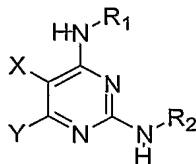
provided that when V is NH₂, X, Y and Z are not simultaneously H.

[0026] In one embodiment, the compounds of the invention comprise those according to formula I wherein V is NHR₁.

[0027] In another embodiment, the compounds of the invention comprise those according to formula I wherein Z is NR₂R₃.

[0028] In another embodiment of the compounds of formula I, V is NHR_1 and Z is NR_2R_3 .

[0029] The present invention also comprises compounds for modulating IGF1R enzymatic activity, according to Formula II,



II

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R_1 is H, CN, halo, $-\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{NR}_{13}\text{R}_{14}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6$ alkyl- R_{20} , wherein R_{20} is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, $\text{C}_3\text{-C}_7$ heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from $\text{C}_1\text{-C}_6$ alkyl, and $-\text{C}_0\text{-C}_6$ alkyl- R_{21} ;

X is H, halo, $\text{C}_1\text{-C}_6$ alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O-}$ $\text{C}_1\text{-C}_6$ alkyl, or $\text{N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl;

Y is H, halo, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{O-}$ $\text{C}_1\text{-C}_6$ alkyl, $-\text{O-}(\text{CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6\text{-alkyl-}$ R_{21} , $-\text{O-}$ R_{21} , $-\text{C}(\text{O})\text{-}$ R_{21} , $-\text{O-}(\text{CH}_2)_n\text{-}$ R_{21} , $-\text{C}(\text{O})\text{-NR}_{13}\text{R}_{14}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-aryl}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-aryl}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-heterocyclyl}$, wherein R_{21} is heterocyclyl, aryl, heteroaryl, or $\text{C}_3\text{-C}_7$ cycloalkyl, and wherein alkyl, aryl, heteroaryl, $\text{C}_3\text{-C}_7$ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{NR}_{13}\text{R}_{14}$, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, $\text{C}_1\text{-C}_6$ alkyl, aryl- $\text{C}_1\text{-C}_6$ alkyl-, aryl- $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_n\text{-aryl-}$, arylOH, $\text{C}_3\text{-C}_7$ cycloalkyl, heterocyclyl, $-\text{aryl-N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_3\text{-C}_7$ cycloalkyl- $\text{C}(\text{O})\text{-N}(\text{R}_{14})\text{-aryl}$, and a group of the formula $-\text{L-M-Q}$, wherein

L is a bond or $\text{C}_3\text{-C}_7$ cycloalkyl,

M is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, or $\text{C}_2\text{-C}_6$ alkynyl,

Q is $\text{NR}_{13}\text{R}_{14}$, $\text{N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, $\text{C}(\text{O})\text{O}(\text{CH}_2)_n\text{-phenyl}$, and $\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl;

R_2 is $\text{-C}_1\text{-C}_6$ alkyl, $\text{-C}_1\text{-C}_6$ alkyl- $\text{NR}_{13}\text{R}_{14}$, $\text{-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-heteroaryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-(C}_3\text{-C}_7\text{-cycloalkyl)}$, $\text{-C}_0\text{-C}_6\text{-alkyl-heterocyclyl}$, or $\text{-C}_0\text{-C}_6\text{-alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each alkyl is optionally substituted with phenyl, and each aryl, heteroaryl, C}_3\text{-C}_7\text{ cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO}_2\text{, NR}_{13}\text{R}_{14}\text{, C}(\text{O})\text{O-C}_1\text{-C}_6\text{ alkyl, N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{ alkyl, -SO}_2\text{NR}_{13}\text{R}_{14}\text{, -O-C}(\text{O})\text{-NR}_{13}\text{R}_{14}\text{, -C}_0\text{-C}_6\text{ alkyl-C}(\text{O})\text{NR}_{15}\text{R}_{16}\text{, C}_1\text{-C}_6\text{ alkoxy, C}_1\text{-C}_6\text{ thioalkoxy, -O-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}\text{, -C}_1\text{-C}_6\text{ alkyl-NR}_{13}\text{R}_{14}\text{, -N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_1\text{-C}_6\text{ alkyl, -N}(\text{R}_{13})\text{-C}(\text{O})\text{-aryl, -C}_0\text{-C}_6\text{ alkyl-C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}\text{, -C}_0\text{-C}_6\text{ alkyl-C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-aryl, -O-(CH}_2)_n\text{-C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}\text{, -O-(CH}_2)_n\text{-C}(\text{O})\text{-NR}_{15}\text{R}_{16}\text{, -C}_0\text{-C}_6\text{ alkyl-C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-O-C}_1\text{-C}_6\text{ alkyl, -C}_0\text{-C}_6\text{ alkyl-N}(\text{R}_{13})\text{-C}(\text{O})\text{O-C}_1\text{-C}_6\text{ alkyl, -C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heterocyclyl, -C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heteroaryl, -C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-aryl, -C}_0\text{-C}_6\text{-alkyl-R}_{21}\text{, aryloxy, -O-(CH}_2)_n\text{-R}_{21}\text{, -SO}_2\text{-heterocyclyl, N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_3\text{-C}_7\text{-cycloalkyl, -C}_0\text{-C}_6\text{alkyl C}(\text{O})\text{O-R}_{21}\text{, C}_3\text{-C}_7\text{-cycloalkyl, -C}_0\text{-C}_6\text{alkylR}_{21}\text{, -SC}_1\text{-C}_6\text{alkyl or C}_1\text{-C}_6\text{ alkyl optionally substituted with halo or cyano,}$

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{NR}_{13}\text{R}_{14}$ and $\text{C}_1\text{-C}_6$ alkoxy;

R_{13} and R_{14} are independently H or $\text{C}_1\text{-C}_6$ alkyl, or R_{13} and R_{14} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ alkoxy;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or -C(O)O-C₁-C₆ alkyl; and

n is 1-6.

[0030] In a preferred embodiment of the compound according to formula II, X is H, C₁-C₆ alkyl, or halo.

[0031] In another preferred embodiment of the compound according to formula II, X is H or halo.

[0032] In another preferred embodiment of the compound according to formula II, X is halo. Preferably, the halo is Cl or Br, more preferably Br.

[0033] In another preferred embodiment of the compound according to formula II, Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-R₂₁, -O-(CH₂)_n-R₂₁, or aryl.

[0034] In another preferred embodiment of the compound according to formula II, Y is H.

[0035] In another preferred embodiment of the compound according to formula II, Y is halo, preferably bromo or chloro, more preferably bromo.

[0036] In another preferred embodiment of the compound according to formula II, Y is C₁-C₆ alkyl, preferably C₁-C₃ alkyl, more preferably methyl.

[0037] In another preferred embodiment of the compound according to formula II, R₁ is aryl or heteroaryl optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, and heteroaryl.

[0038] In another preferred embodiment of the compound according to formula II, R₁ is heteroaryl, optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, and heteroaryl.

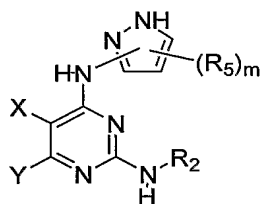
[0039] In another preferred embodiment of the compound according to formula II, R₁ is pyrazolyl or isoxazolyl, optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, and heteroaryl.

[0040] In another preferred embodiment of the compound according to formula II, R₂ is aryl or -C₁-C₆-alkyl-heteroaryl, wherein aryl or heteroaryl are optionally substituted as defined above for compounds of formula II.

[0041] In another preferred embodiment of the compound according to formula II, R_2 is C_1 - C_6 -alkyl-heteroaryl, optionally substituted as defined above for compounds of formula II. Preferably, R_2 is C_1 - C_2 -isoxazolyl, optionally substituted with aryl, heterocyclyl, or C_1 - C_6 alkyl.

[0042] In another preferred embodiment of the compound according to formula II, R_2 is aryl, optionally substituted as defined above for compounds of formula II. Preferably, R_2 is phenyl, optionally substituted with $-O-(CH_2)_n-NR_{15}R_{16}$, $NR_{13}R_{14}$, $-C_0$ - C_6 alkyl- $C(O)NR_{15}R_{16}$, $-C_0$ - C_6 alkyl- $C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $N(R_{13})C(O)-C_1$ - C_6 alkyl, halo, $-C_1$ - C_6 alkyl- $NR_{13}R_{14}$, C_1 - C_6 alkoxy, or heterocyclyl.

[0043] The present invention comprises a compound for modulating protein kinase enzymatic activity, according to Formula III,



III

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

m is 1 or 2;

R_5 at each occurrence is independently H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl;

X is H, halo, C_1 - C_6 alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $NR_{13}R_{14}$, $C(O)O$ - C_1 - C_6 alkyl, or $N(R_{13})-C(O)-C_1$ - C_6 alkyl;

Y is H, halo, OH, C_1 - C_6 alkyl, $NR_{15}R_{16}$, C_1 - C_6 alkoxy, $-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C(O)O-C_1$ - C_6 alkyl, $-O-(CH_2)_n-NR_{15}R_{16}$, $-C(O)-C_1$ - C_6 alkyl, $-C_0$ - C_6 -alkyl- R_{21} , $-O-R_{21}$, $-C(O)-R_{21}$, $-O-(CH_2)_n-R_{21}$, $-C(O)-NR_{13}R_{14}$, $-C(O)-N(R_{13})$ -aryl, $-C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C(O)-N(R_{13})-(CH_2)_n$ -aryl, $-C(O)-N(R_{13})-(CH_2)_n$ -heterocyclyl, wherein R_{21} is heterocyclyl, aryl, heteroaryl, or C_3 - C_7 cycloalkyl, and wherein alkyl, aryl, heteroaryl, C_3 - C_7 cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C_1 - C_6 alkyl, $NR_{13}R_{14}$, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyl-, aryl- $(CH_2)_n$ -O-aryl-, C_3 - C_7 cycloalkyl, heterocyclyl, -aryl-

$N(R_{13})C(O)-C_3-C_7$ cycloalkyl- $C(O)-N(R_{14})$ -aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C_3-C_7 cycloalkyl,

M is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl,

Q is $NR_{13}R_{14}$, $N(R_{13})C(O)-C_1-C_6$ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, $C(O)O-(CH_2)_n$ -phenyl, and $C(O)-C_1-C_6$ alkyl;

R_2 is $-C_1-C_6$ alkyl, $-C_1-C_6$ alkyl- $NR_{13}R_{14}$, $-C(O)$ -aryl, $-C_0-C_6$ -alkyl-aryl, $-C_0-C_6$ -alkyl-heteroaryl, $-C_0-C_6$ -alkyl- (C_3-C_7) -cycloalkyl, $-C_0-C_6$ -alkyl-heterocyclyl, or $-C_0-C_6$ alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, C_3-C_7 cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO_2 , $NR_{13}R_{14}$, $C(O)O-C_1-C_6$ alkyl, $N(R_{13})C(O)-C_1-C_6$ alkyl, $-SO_2NR_{13}R_{14}$, $-O-C(O)-NR_{13}R_{14}$, $-C_0-C_6$ alkyl- $C(O)NR_{15}R_{16}$, C_1-C_6 alkoxy, C_1-C_6 thioalkoxy, $-O-(CH_2)_n-NR_{15}R_{16}$, $-C_1-C_6$ alkyl- $NR_{13}R_{14}$, $-N(R_{13})-C(O)-C_1-C_6$ alkyl, $-N(R_{13})-C(O)$ -aryl, $-C_0-C_6$ alkyl- $C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C_0-C_6$ alkyl- $C(O)-N(R_{13})-(CH_2)_n$ -aryl, $-O-(CH_2)_n-C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-O-(CH_2)_n-C(O)-NR_{15}R_{16}$, $-C_0-C_6$ alkyl- $C(O)-N(R_{13})-(CH_2)_n-O-C_1-C_6$ alkyl, $-C_0-C_6$ alkyl- $N(R_{13})-C(O)O-C_1-C_6$ alkyl, $-C_0-C_6$ alkyl- $C(O)$ -heterocyclyl, $-C_0-C_6$ alkyl- $C(O)$ -heteroaryl, $-C_0-C_6$ alkyl- $C(O)$ -aryl, $-C_0-C_6$ -alkyl- R_{21} , aryloxy, $-O-(CH_2)_n-R_{21}$, $-SO_2$ -heterocyclyl, $N(R_{13})-C(O)-C_3-C_7$ -cycloalkyl, or C_1-C_6 alkyl optionally substituted with halo or cyano,,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl, or R_{13} and R_{14} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group

wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy; R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, and -C(O)O-C₁-C₆ alkyl; and n is 1-6.

[0044] In one preferred embodiment of the compound according to formula III, X is H, C₁-C₆ alkyl, or halo.

[0045] In another preferred embodiment of the compound is according to formula III, X is H or halo.

[0046] In another preferred embodiment of the compound according to formula III, X is halo. Preferably, the halo is Cl or Br, more preferably Br.

[0047] In another preferred embodiment of the compound according to formula III, Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-R₂₁, -O-R₂₁, or aryl.

[0048] In another preferred embodiment of the compound according to formula III, Y is H.

[0049] In another preferred embodiment of the compound according to formula III, Y is halo, preferably bromo or chloro, more preferably bromo.

[0050] In another preferred embodiment of the compound according to formula III, Y is C₁-C₆ alkyl, preferably C₁-C₃ alkyl, more preferably methyl.

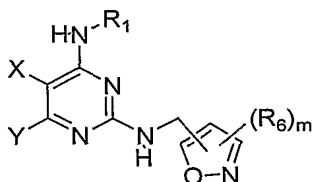
[0051] In another preferred embodiment of the compound according to formula III, R₂ is aryl or -C₁-C₆-alkyl-heteroaryl, wherein aryl or heteroaryl are optionally substituted as defined above for compounds of formula III.

[0052] In another preferred embodiment of the compound according to formula III, R₂ is C₁-C₆-alkyl-heteroaryl, optionally substituted as defined above for compounds of formula III. Preferably, R₂ is C₁-C₂-isoxazolyl, optionally substituted with 1 or 2 of aryl, heterocyclyl, or C₁-C₆ alkyl.

[0053] In another preferred embodiment of the compound according to formula III, R₂ is aryl, optionally substituted as defined above for compounds of formula III. Preferably, R₂ is

phenyl, optionally substituted with 1 or 2 of $-\text{O}-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $\text{NR}_{13}\text{R}_{14}$, $-\text{C}_0-\text{C}_6$ alkyl- $\text{C}(\text{O})\text{NR}_{15}\text{R}_{16}$, $-\text{C}_0-\text{C}_6$ alkyl- $\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $\text{N}(\text{R}_{13})\text{C}(\text{O})-\text{C}_1-\text{C}_6$ alkyl, halo, $-\text{C}_1-\text{C}_6$ alkyl- $\text{NR}_{13}\text{R}_{14}$, C_1-C_6 alkoxy, or heterocyclyl.

[0054] The present invention comprises a compound for modulating IGF1R activity, according to Formula IV,



IV

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R_1 is H, CN, halo, $-\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{NR}_{13}\text{R}_{14}$, C_1-C_6 alkyl, $-\text{C}(\text{O})-\text{C}_1-\text{C}_6$ alkyl, $-\text{C}_0-\text{C}_6$ alkyl- R_{20} , wherein R_{20} is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, C_3-C_7 heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from C_1-C_6 alkyl, and $-\text{C}_0-\text{C}_6$ alkyl- R_{21} ;

X is H, halo, C_1-C_6 alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O}-\text{C}_1-\text{C}_6$ alkyl, or $\text{N}(\text{R}_{13})-\text{C}(\text{O})-\text{C}_1-\text{C}_6$ alkyl;

Y is H, halo, OH, C_1-C_6 alkyl, $\text{NR}_{15}\text{R}_{16}$, C_1-C_6 alkoxy, $-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{O}-\text{C}_1-\text{C}_6$ alkyl, $-\text{O}-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{C}_1-\text{C}_6$ alkyl, $-\text{C}_0-\text{C}_6$ -alkyl- R_{21} , $-\text{O}-\text{R}_{21}$, $-\text{C}(\text{O})-\text{R}_{21}$, $-\text{O}-(\text{CH}_2)_n-\text{R}_{21}$, $-\text{C}(\text{O})-\text{NR}_{13}\text{R}_{14}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-\text{aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n-\text{aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n$ -heterocyclyl, wherein R_{21} is heterocyclyl, aryl, heteroaryl, or C_3-C_7 cycloalkyl, and wherein alkyl, aryl, heteroaryl, C_3-C_7 cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C_1-C_6 alkyl, $\text{NR}_{13}\text{R}_{14}$, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C_1-C_6 alkyl, aryl- C_1-C_6 alkyl-, aryl- $(\text{CH}_2)_n$ -O-aryl-, C_3-C_7 cycloalkyl, heterocyclyl, $-\text{aryl}-\text{N}(\text{R}_{13})\text{C}(\text{O})-\text{C}_3-\text{C}_7$ cycloalkyl- $\text{C}(\text{O})-\text{N}(\text{R}_{14})-\text{aryl}$, and a group of the formula $-\text{L}-\text{M}-\text{Q}$, wherein

L is a bond or C_3-C_7 cycloalkyl,

M is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl,

Q is $\text{NR}_{13}\text{R}_{14}$, $\text{N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, and heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties selected from halo, $\text{C}(\text{O})\text{O}(\text{CH}_2)_n\text{-phenyl}$, and $\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl;

R_6 at each occurrence is independently H, halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO_2 , $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, $\text{N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, - $\text{SO}_2\text{NR}_{13}\text{R}_{14}$, $\text{-O-C}(\text{O})\text{-NR}_{13}\text{R}_{14}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ thioalkoxy, $\text{-O-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_1\text{-C}_6$ alkyl- $\text{NR}_{13}\text{R}_{14}$, $\text{-N(R}_{13})\text{-C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, - $\text{N(R}_{13})\text{-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N(R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N(R}_{13})\text{-(CH}_2)_n\text{-aryl}$, $\text{-O-(CH}_2)_n\text{-C}(\text{O})\text{-N(R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-O-(CH}_2)_n\text{-C}(\text{O})\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N(R}_{13})\text{-(CH}_2)_n\text{-O-C}_1\text{-C}_6$ alkyl, $\text{-C}_0\text{-C}_6$ alkyl- $\text{N(R}_{13})\text{-C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, $\text{-C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heterocyclyl}$, $\text{-C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heteroaryl}$, - $\text{C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-R}_{21}$, aryloxy, $\text{-O-(CH}_2)_n\text{-R}_{21}$, $\text{-SO}_2\text{-heterocyclyl}$, $\text{N(R}_{13})\text{-C}(\text{O})\text{-C}_3\text{-C}_7\text{-cycloalkyl}$, or $\text{C}_1\text{-C}_6$ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ alkoxy;

R_{13} and R_{14} are independently H or $\text{C}_1\text{-C}_6$ alkyl, or R_{13} and R_{14} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ alkoxy;

R_{15} and R_{16} are independently H, $\text{C}_1\text{-C}_6$ alkyl, heteroaryl, or heterocyclyl, or R_{15} and R_{16} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties selected from halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{-C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl; and

m is 1 or 2; and n is 1-6.

[0055] In one preferred embodiment of the compound according to formula IV, X is H, C₁-C₆ alkyl, or halo.

[0056] In another preferred embodiment of the compound according to formula IV, X is H or halo.

[0057] In another preferred embodiment of the compound according to formula IV, X is halo. Preferably, the halo is Cl or Br, more preferably Br.

[0058] In another preferred embodiment of the compound according to formula IV, Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-R₂₁, -O-R₂₁, or aryl.

[0059] In another preferred embodiment of the compound according to formula IV, Y is H.

[0060] In another preferred embodiment of the compound according to formula IV, Y is halo, preferably bromo or chloro, more preferably bromo.

[0061] In another preferred embodiment of the compound according to formula IV, Y is C₁-C₆ alkyl, preferably C₁-C₃ alkyl, more preferably methyl.

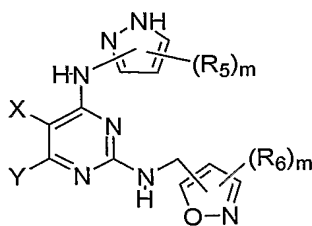
[0062] In another preferred embodiment of the compound according to formula IV, R₁ is aryl or heteroaryl optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, or heteroaryl.

[0063] In another preferred embodiment of the compound according to formula IV, R₁ is heteroaryl, optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, or heteroaryl.

[0064] In another preferred embodiment of the compound according to formula IV, R₁ is pyrazolyl or isoxazolyl, optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, or heteroaryl.

[0065] In another preferred embodiment of the compound according to formula IV, m is 1 and R₆ is aryl, heterocyclyl, or C₁-C₆ alkyl.

[0066] The present invention comprises a compound for modulating protein kinase enzymatic activity, according to Formula V,



V

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

m is independently 1 or 2;

R₅ at each occurrence is independently H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, or heteroaryl;

X is H, halo, C₁-C₆ alkyl, NO₂, mono-, di-, or tri-halo substituted methyl, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, or N(R₁₃)-C(O)-C₁-C₆ alkyl;

Y is H, halo, OH, C₁-C₆ alkyl, NR₁₅R₁₆, C₁-C₆ alkoxy, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -C(O)-C₁-C₆ alkyl, -C₀-C₆-alkyl-R₂₁, -O-R₂₁, -C(O)-R₂₁, -O-(CH₂)_n-R₂₁, -C(O)-NR₁₃R₁₄, -C(O)-N(R₁₃)-aryl, -C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)-N(R₁₃)-(CH₂)_n-aryl, -C(O)-N(R₁₃)-(CH₂)_n-heterocyclyl, wherein R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, aryl-C₁-C₆ alkyl-, aryl-(CH₂)_n-O-aryl-, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is NR₁₃R₁₄, N(R₁₃)C(O)-C₁-C₆ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties selected from halo, C(O)O-(CH₂)_n-phenyl, and C(O)-C₁-C₆ alkyl;

R₆ at each occurrence is independently H, halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO₂, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, N(R₁₃)C(O)-C₁-

C₆ alkyl, -SO₂NR₁₃R₁₄, -O-C(O)-NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, -O-(CH₂)_n-NR₁₅R₁₆, -C₁-C₆ alkyl-NR₁₃R₁₄, -N(R₁₃)-C(O)-C₁-C₆ alkyl, -N(R₁₃)-C(O)-aryl, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-aryl, -O-(CH₂)_n-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-C(O)-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-O-C₁-C₆ alkyl, -C₀-C₆ alkyl-N(R₁₃)-C(O)O-C₁-C₆ alkyl, -C₀-C₆alkyl-C(O)-heterocyclyl, -C₀-C₆alkyl-C(O)-heteroaryl, -C₀-C₆alkyl-C(O)-aryl, -C₀-C₆-alkyl-R₂₁, aryloxy, -O-(CH₂)_n-R₂₁, -SO₂-heterocyclyl, N(R₁₃)-C(O)-C₃-C₇-cycloalkyl, or C₁-C₆ alkyl optionally substituted with halo or cyano, wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally

substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

R₁₃ and R₁₄ are independently H or C₁-C₆ alkyl, or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, and -C(O)O-C₁-C₆ alkyl; and

n is 1-6.

[0067] In one preferred embodiment of the compound according to formula V, X is H, C₁-C₆ alkyl, or halo.

[0068] In another preferred embodiment of the compound according to formula V, X is H or halo.

[0069] In another preferred embodiment of the compound according to formula V, X is halo. Preferably, halo is Cl or Br, more preferably Br.

[0070] In another preferred embodiment of the compound according to formula V, Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-R₂₁, -O-R₂₁, or aryl.

[0071] In another preferred embodiment of the compound according to formula V, Y is H.

[0072] In another preferred embodiment of the compound according to formula V, Y is halo, preferably bromo or chloro, more preferably bromo.

[0073] In another preferred embodiment of the compound according to formula V, Y is C₁-C₆ alkyl, preferably C₁-C₃ alkyl, more preferably methyl.

[0074] In another preferred embodiment of the compound according to formula V, m is 1 and R₆ is aryl, heterocyclyl, or C₁-C₆ alkyl.

[0075] The present invention also comprises a compound for modulating protein kinase enzymatic activity, according to Formula I, wherein,

V is NR₁R_{1a},

R₁ is -C₀-C₆ alkyl-R₂₀, wherein R₂₀ heteroaryl, wherein the heteroaryl is optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, and -C₀-C₆ alkyl-R₂₁;

R_{1a} is H;

X is H, or halo;

Y is H, C₁-C₆ alkyl, NR₁₅R₁₆, C₀-C₆ alkyl-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆-alkyl-R₂₁, -O-R₂₁ or -O-(CH₂)_n-R₂₁;

Z is NR₂R₃, or -O-R_{2a}, wherein

R₂ is -C₀-C₆-alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with one, two, or three groups independently selected from -C₀-C₆-alkyl-R₂₁ or C₁-C₆ alkyl;

R₃ is H;

R_{2a} is C₀-C₆ alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with aryl;

R₁₃ is H;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl or heterocyclyl optionally substituted with C₁-C₆ alkyl;

R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl or NR₁₃R₁₄; and

n is 1-4.

[0076] In another preferred embodiment of the compound according to formula 1, Z is NR₂R₃, wherein R₂ is -C₁-C₃-alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with R₂₁ or C₁-C₄ alkyl. Preferably, the C₁-C₄ alkyl is methyl, propyl or isopropyl. Also

preferred are compounds wherein the R_{21} is heteroaryl or aryl wherein the heteroaryl and aryl are optionally substituted with halo or NH_2 . Preferably, the halo is fluoro.

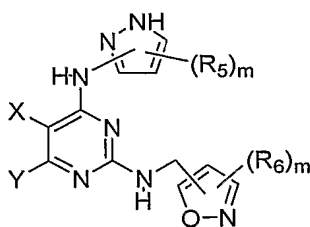
[0077] In another preferred embodiment of the compound according to formula 1, Z is $-O-R_{2a}$, wherein R_{2a} is C_1 - C_2 alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with phenyl.

[0078] In another preferred embodiment of the compound according to formula 1, R_1 is heteroaryl optionally substituted with C_1 - C_4 alkyl or R_{21} . Preferably, the C_1 - C_4 alkyl is methyl, propyl, isopropyl. Also preferred are compounds wherein R_{21} is C_3 - C_4 cycloalkyl. Preferably, R_{21} is cyclopropyl.

[0079] In another preferred embodiment of the compound according to formula 1, X is chloro.

[0080] In another preferred embodiment of the compound according to formula 1, Y is C_1 - C_4 alkyl, $NR_{15}R_{16}$, C_1 - C_4 alkyl- $NR_{15}R_{16}$, $-N(H)-(CH_2)_{2-3}-NR_{15}R_{16}$, $-O-(CH_2)_2-NR_{15}R_{16}$, $-R_{21}$, $-O-R_{21}$ or $-O-(CH_2)_2-R_{21}$. Preferably, R_{15} and R_{16} are independently H, C_1 - C_4 alkyl or heterocyclyl optionally substituted with C_1 - C_3 alkyl. More preferably, R_{15} and R_{16} are independently methyl, ethyl, propyl, heterocyclyl optionally substituted with methyl, ethyl or propyl. Also preferred are compounds wherein R_{21} is heterocyclyl optionally substituted with one or two moieties independently selected from $-S(O)_2-C_1$ - C_3 alkyl, $-C(O)-C_1$ - C_3 alkyl, $-C(O)-H$, C_1 - C_2 alkyl-aryl, or C_1 - C_4 alkyl. Preferably, R_{21} is optionally substituted with one or two moieties independently selected from $-S(O)_2-CH_3$, $-C(O)-CH_3$, $-CH_2$ -phenyl, methyl, ethyl or propyl.

[0081] The present invention also comprises a compound for modulating protein kinase enzymatic activity, according to Formula VI,



VI

wherein,

m is 1 or 2 or 3;

R_5 is C_1 - C_6 alkyl, and $-C_0$ - C_6 alkyl- R_{21} ;

X is H, or halo;

Y is $-C_0$ - C_6 -alkyl- R_{21} ;

R₆ is -C₀-C₆-alkyl-R₂₁ or C₁-C₆ alkyl;

R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl or NR₁₃R₁₄.

[0082] In another preferred embodiment of the compound according to formula VI, Y is heterocyclyl optionally substituted with C₁-C₃ alkyl, X is H or halo, R₅ is C₃-C₄ cycloalkyl and R₆ is C₁-C₄ alkyl. Preferably, Y is heterocyclyl optionally substituted with methyl, ethyl, propyl or isopropyl, X is H, R₅ is cyclopropyl and R₆ is methyl, ethyl, propyl or isopropyl.

[0083] In another preferred embodiment the compound is selected from compounds listed in Tables 1 and 1a, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

Table 1

“Abs” refers to absolute stereochemistry.

| Entry | Structure |
|-------|-----------|
| 1 | |
| 2 | |
| 3 | |
| 4 | |

| Entry | Structure |
|-------|-----------|
| 5 | |
| 6 | |
| 7 | |
| 8 | |

| Entry | Structure |
|-------|-----------|
| 9 | |
| 10 | |
| 11 | |
| 12 | |
| 13 | |
| 14 | |

| Entry | Structure |
|-------|-----------|
| 15 | |
| 16 | |
| 17 | |
| 18 | |
| 19 | |
| 20 | |

| Entry | Structure |
|-------|-----------|
| 21 | |
| 22 | |
| 23 | |
| 24 | |
| 25 | |
| 26 | |

| Entry | Structure |
|-------|-----------|
| 27 | |
| 28 | |
| 29 | |
| 30 | |
| 31 | |
| 32 | |
| 33 | |

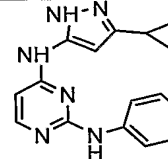
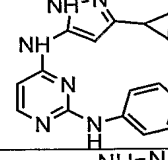
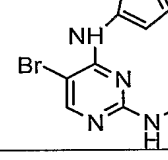
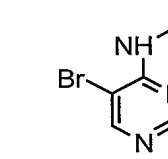
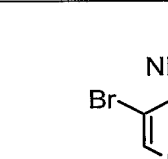
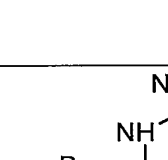
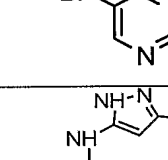
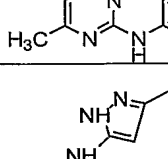
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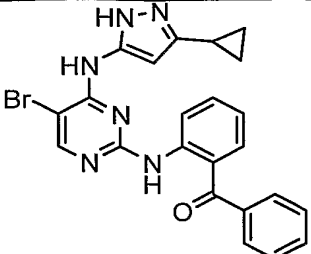
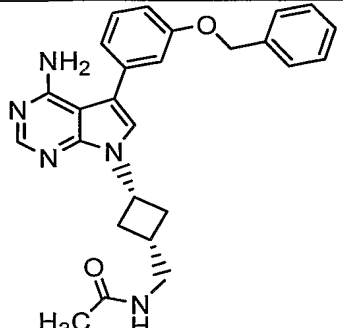
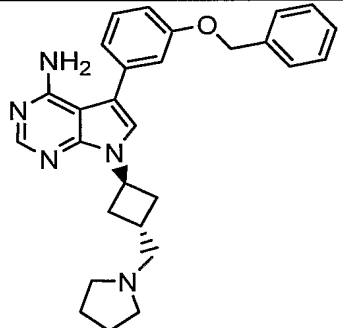
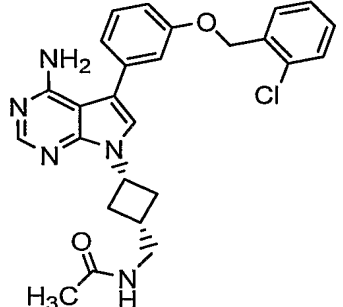
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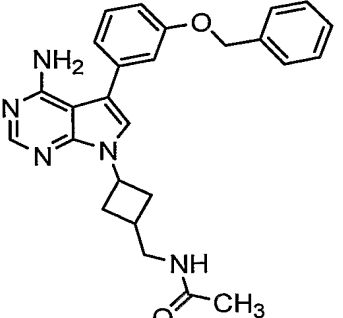
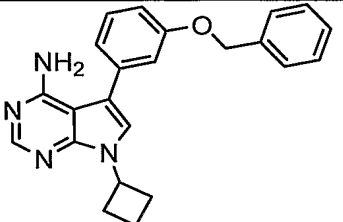
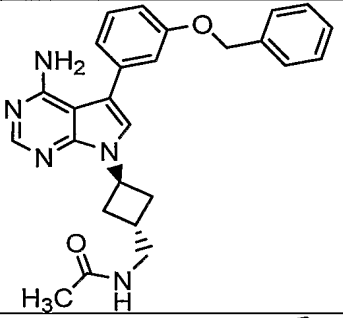
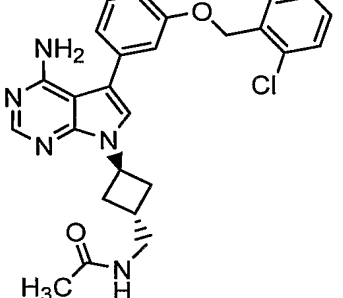
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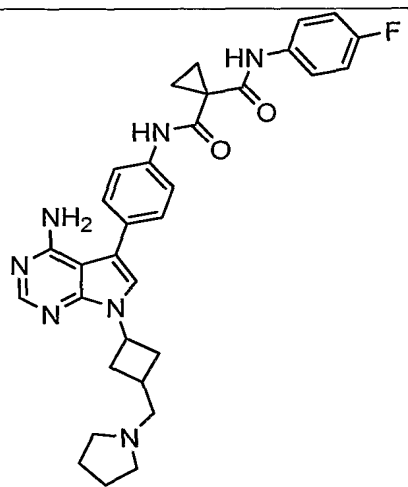
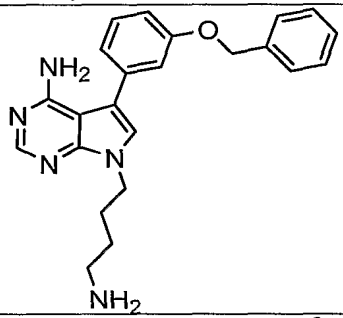
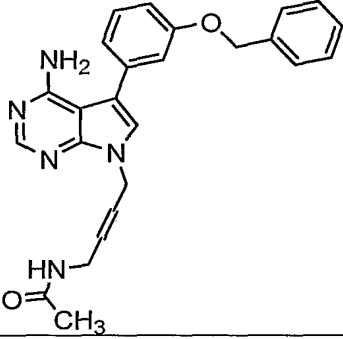
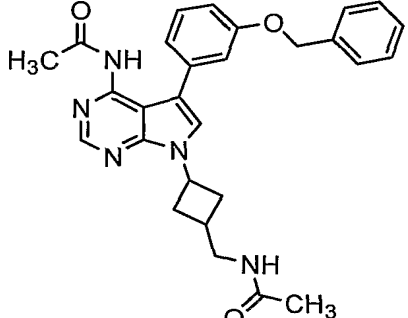
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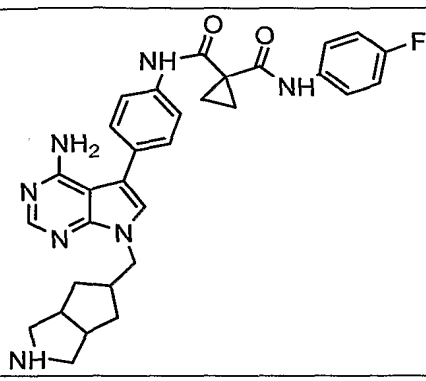
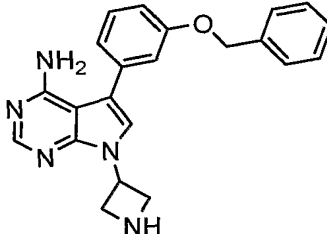
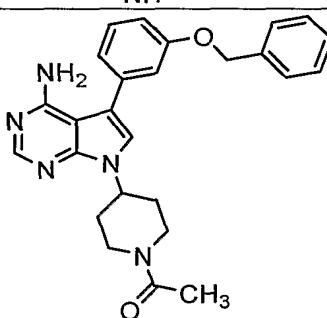
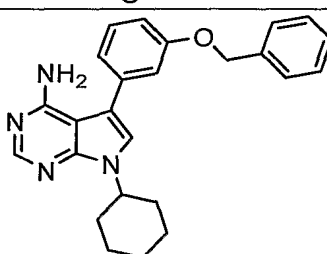
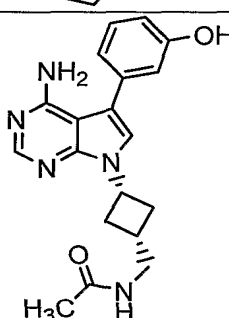
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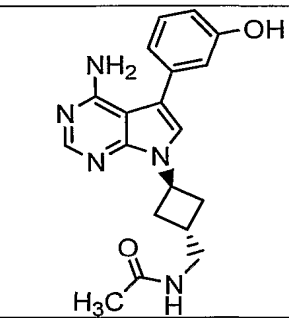
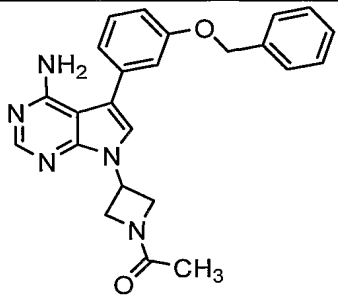
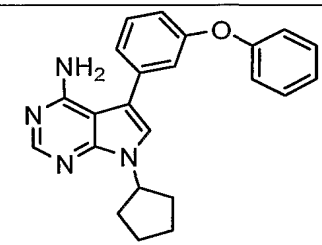
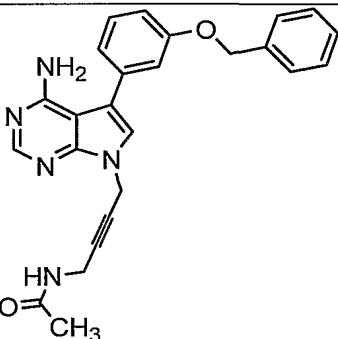
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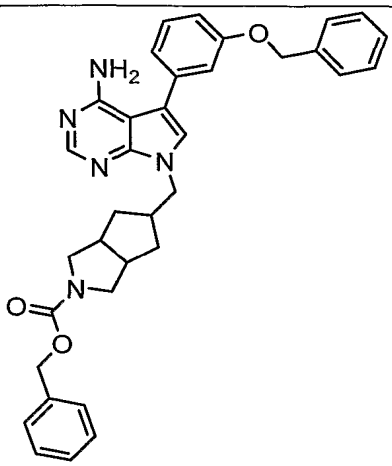
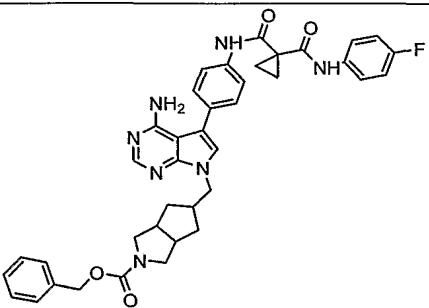
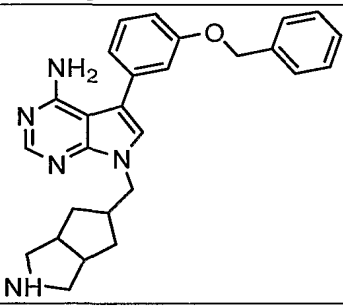
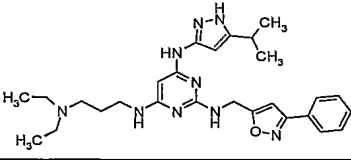
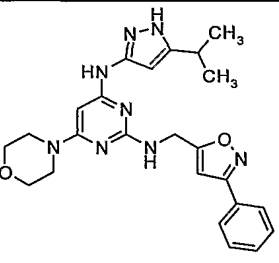
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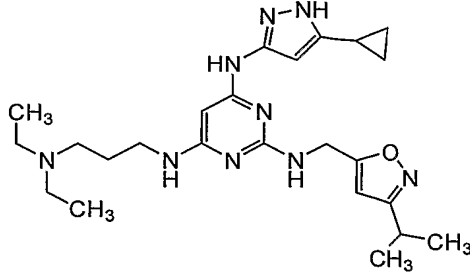
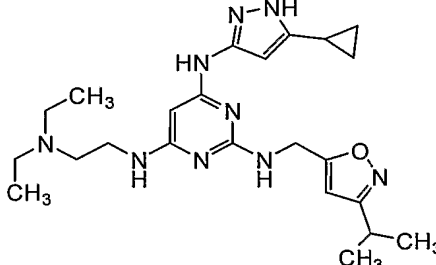
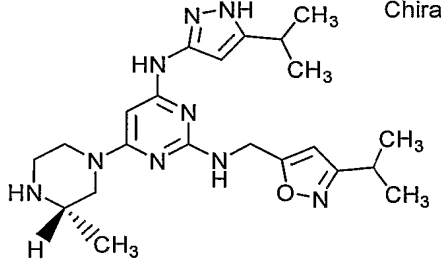
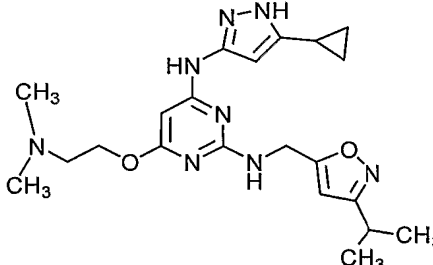
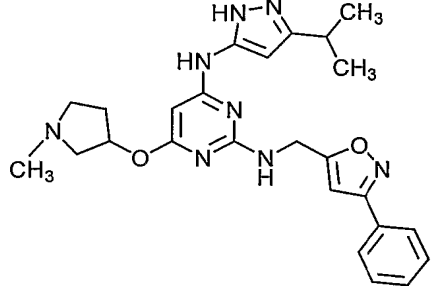
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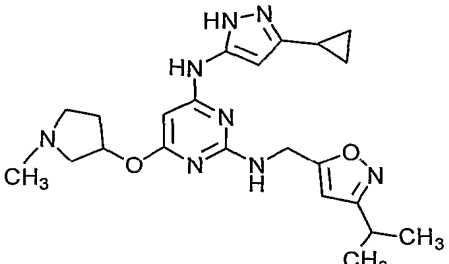
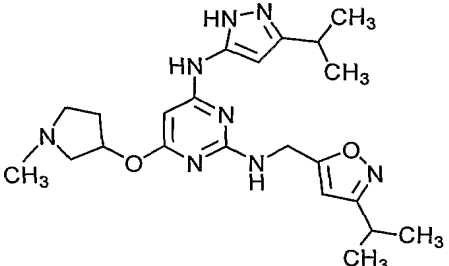
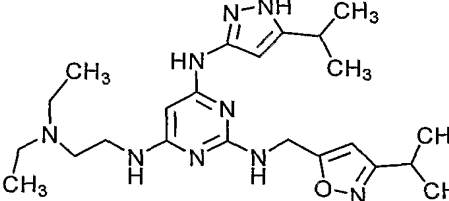
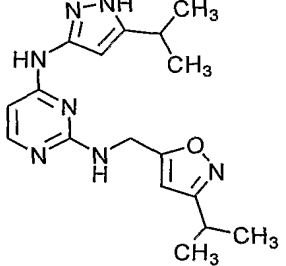
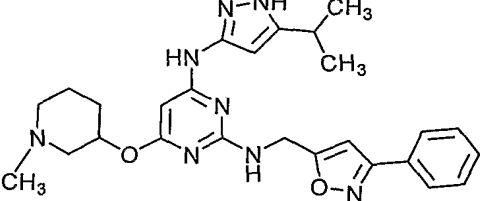
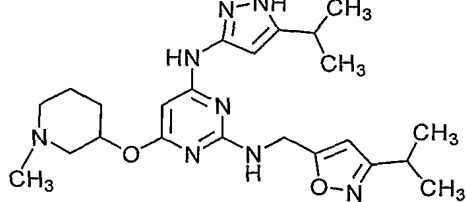
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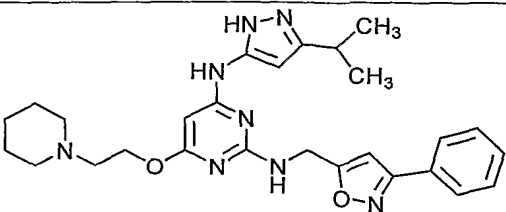
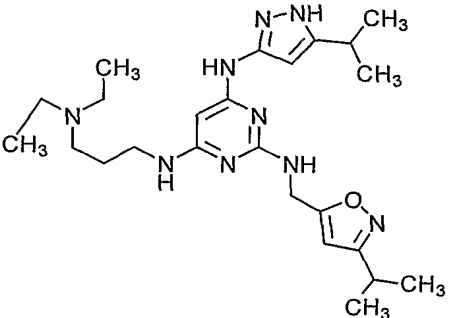
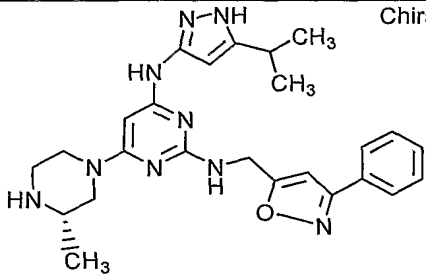
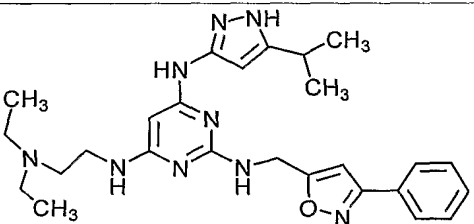
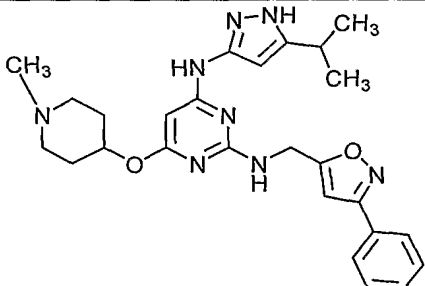
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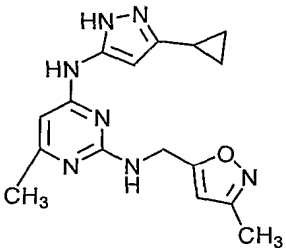
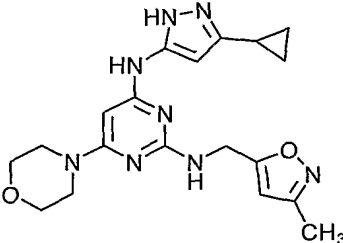
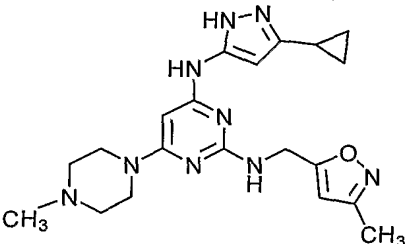
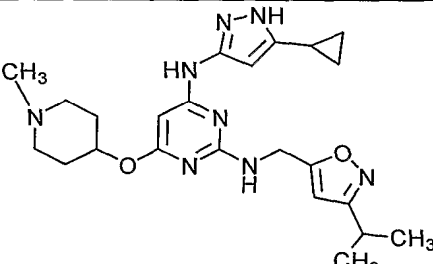
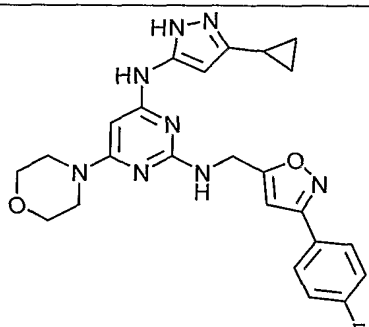
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| 573 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^6 -[3-(diethylamino)propyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |
| 574 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^6 -[2-(diethylamino)ethyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |
| 575 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine |
| 576 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 577 |  | N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

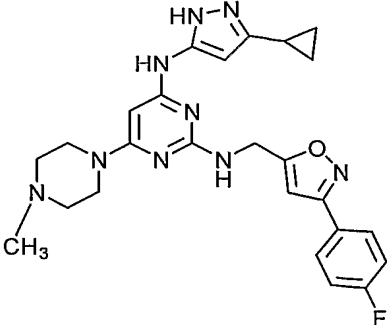
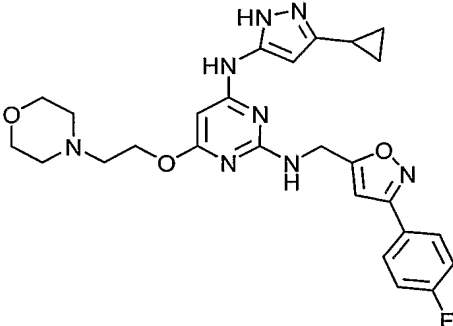
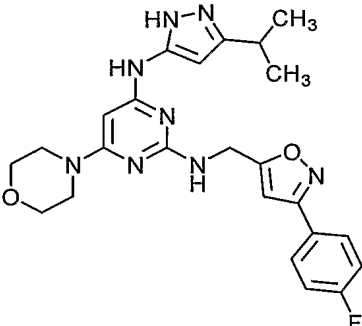
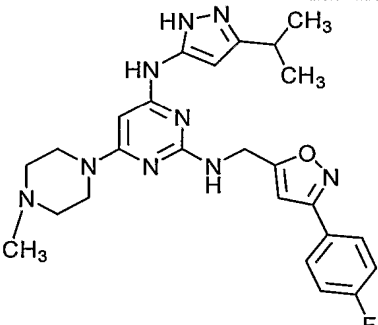
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| 578 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 579 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 580 |  | N^4 -[2-(diethylamino)ethyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4,6-triamine |
| 581 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4-diamine |
| 582 |  | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 583 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine |

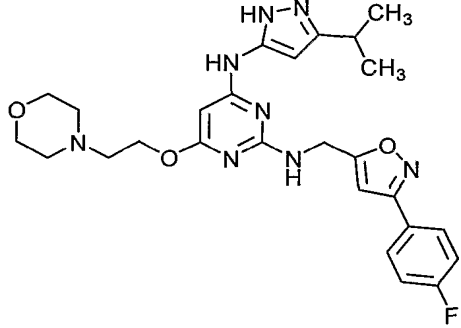
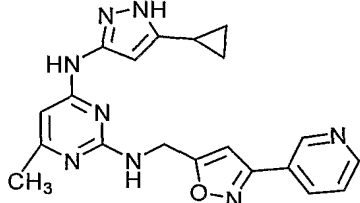
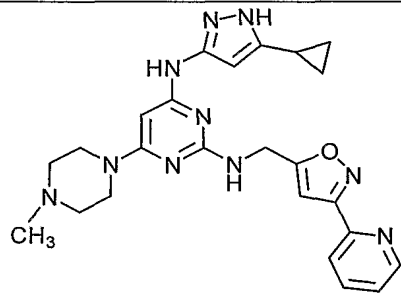
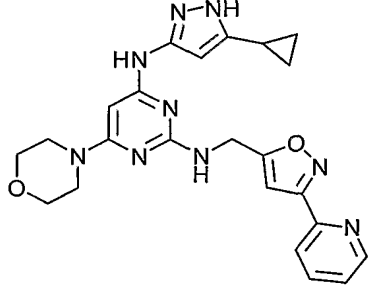
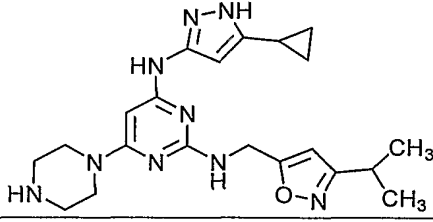
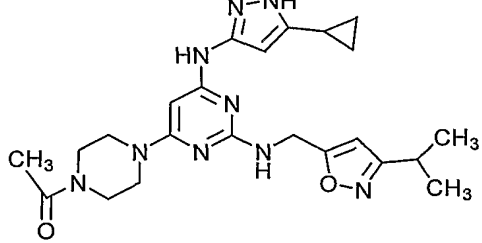
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| 584 | | N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-2-[(3-phenylisoxazol-5-yl)methyl]oxy pyrimidin-4-amine |
| 585 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(4-phenyl-1H-imidazol-2-yl)methyl]pyrimidine-2,4-diamine |
| 586 | | 6-{[2-(dimethylamino)ethyl]oxy}-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4-diamine |
| 587 | | N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 588 | | N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

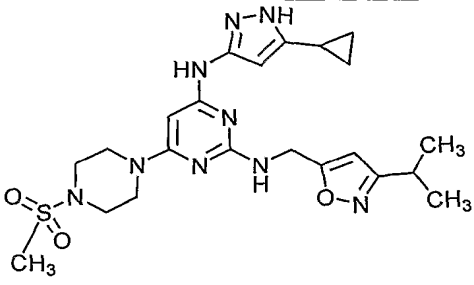
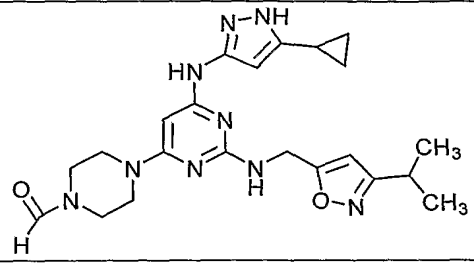
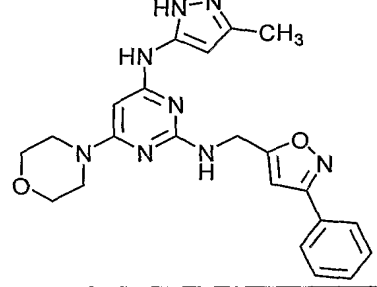
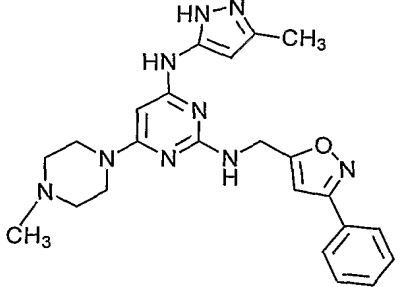
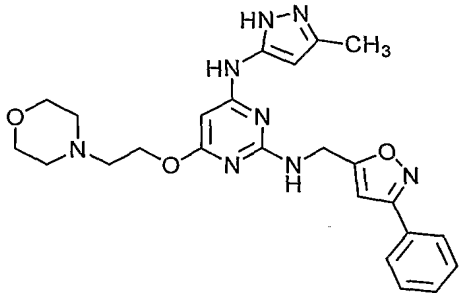
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| 589 |  | N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 590 |  | N^4 -[3-(diethylamino)propyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl)methyl]- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4,6-triamine |
| 591 |  Chiral | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(3S)-3-methylpiperazin-1-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 592 |  | N^4 -[2-(diethylamino)ethyl]- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 593 |  | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-4-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

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| 594 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 595 | | N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 596 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-[3-(diethylamino)propyl]-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 597 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 598 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 599 | | N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpiperidin-4-yl)oxy]pyrimidine-2,4-diamine |

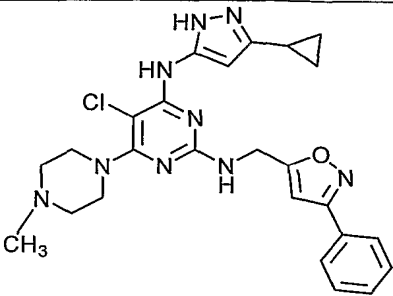
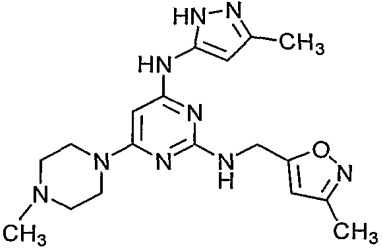
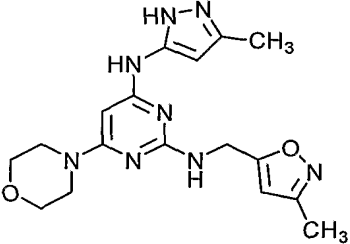
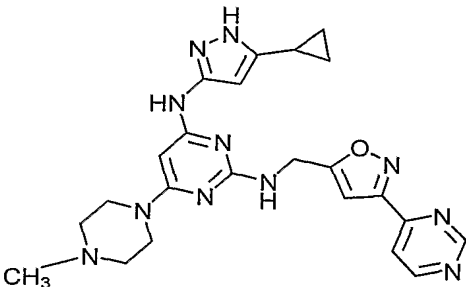
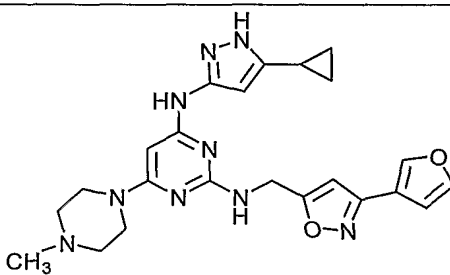
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| 600 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 601 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 602 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 603 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-4-yl)methyl]pyrimidine-2,4-diamine |
| 604 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-morpholin-4-ylpyrimidine-2,4-diamine |

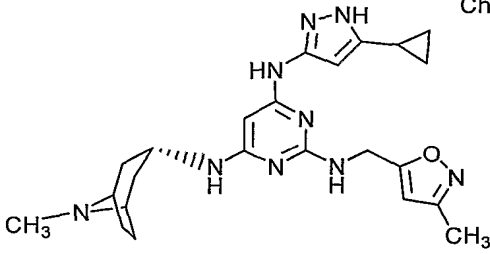
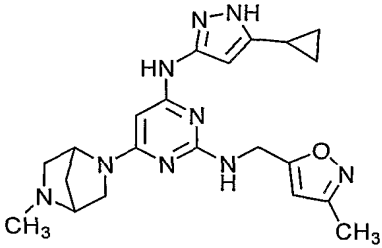
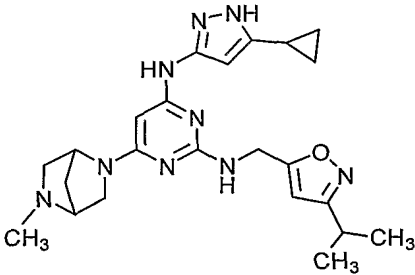
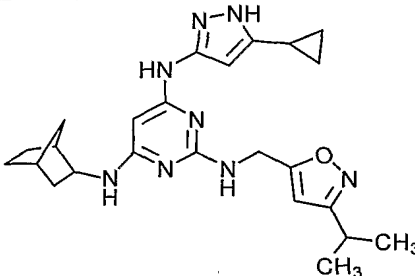
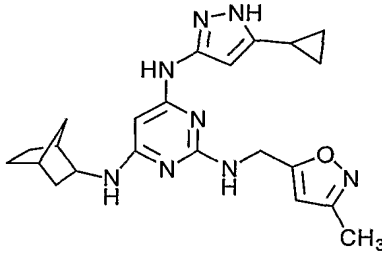
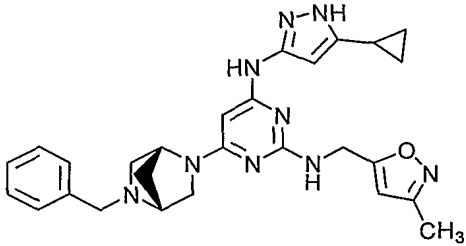
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| 605 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 606 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 607 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 608 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |

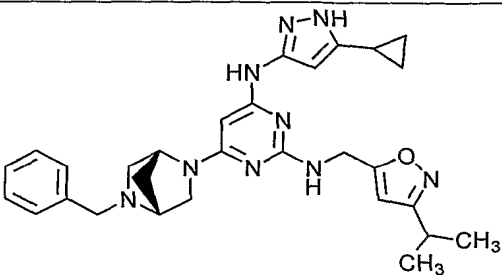
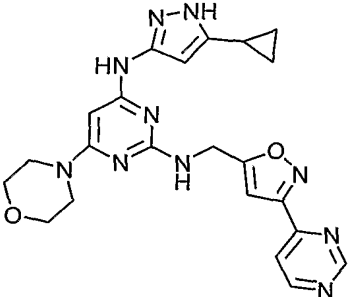
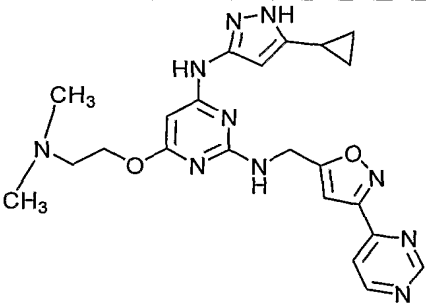
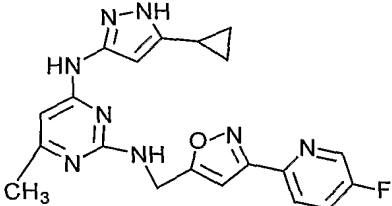
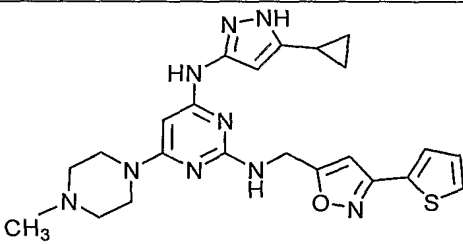
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| 609 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 610 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl- N^2 -[(3-pyridin-3-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 611 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 612 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-morpholin-4-yl- N^2 -[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 613 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-piperazin-1-ylpyrimidine-2,4-diamine |
| 614 |  | 6-(4-acetylpiperazin-1-yl)- N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |

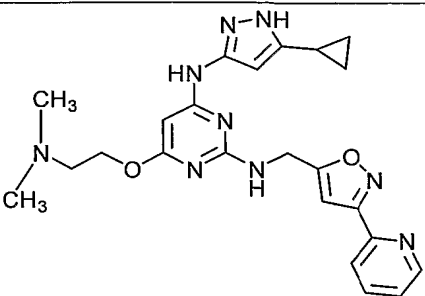
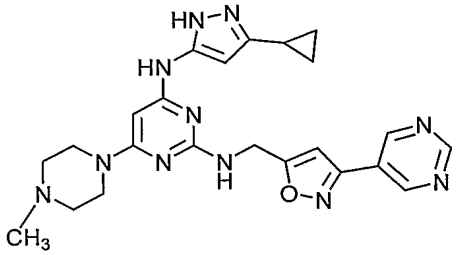
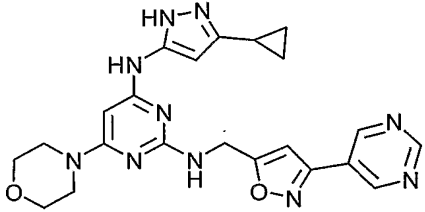
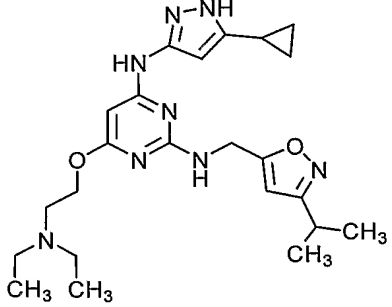
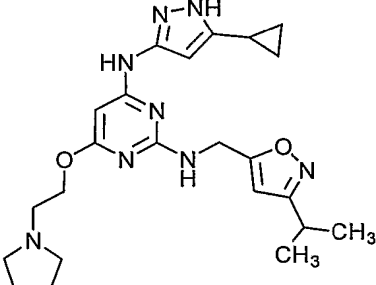
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| 615 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[4-(methylsulfonyl)piperazin-1-yl]pyrimidine-2,4-diamine |
| 616 |  | 4-{6-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperazine-1-carbaldehyde |
| 617 |  | N^4 -(3-methyl-1H-pyrazol-5-yl)-6-morpholin-4-yl- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 618 |  | 6-(4-methylpiperazin-1-yl)- N^4 -(3-methyl-1H-pyrazol-5-yl)- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 619 |  | N^4 -(3-methyl-1H-pyrazol-5-yl)-6-[(2-morpholin-4-ylethyl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

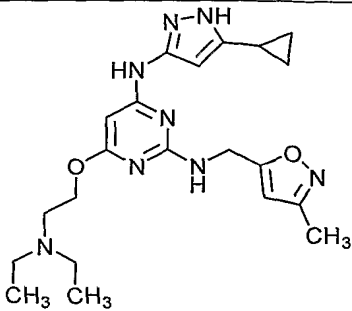
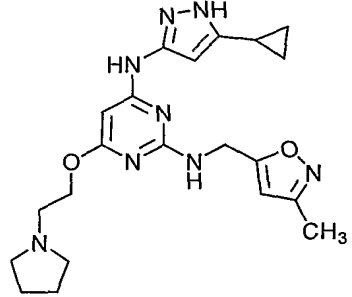
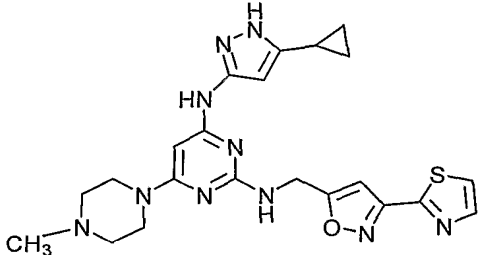
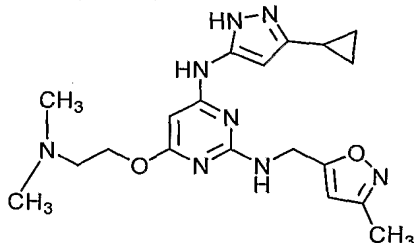
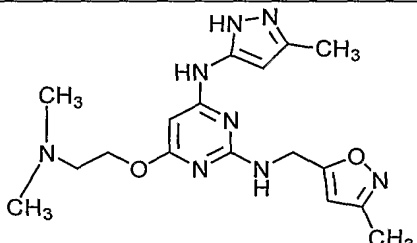
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| 620 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(3-pyridin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 621 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(3,4-difluorophenyl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine |
| 622 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(2,4-difluorophenyl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine |
| 623 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(3-pyrazin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 624 | | 5-chloro-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-morpholin-4-yl-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

| | | |
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| 625 |  | 5-chloro-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 626 |  | N ² -[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)-N ⁴ -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |
| 627 |  | N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 628 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N ² -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 629 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -[(3-furan-3-ylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |

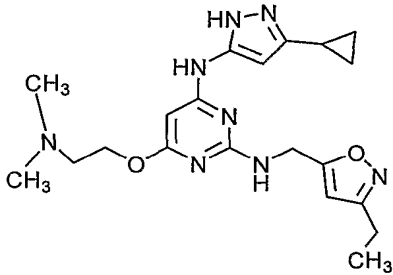
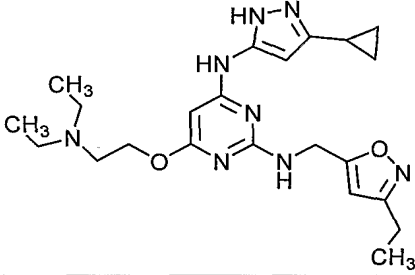
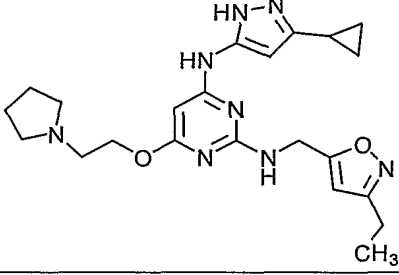
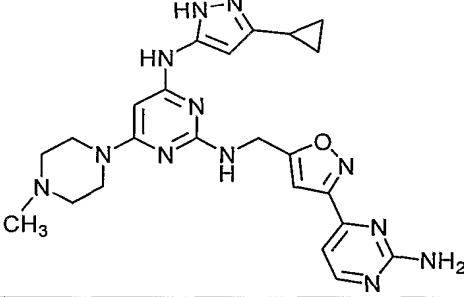
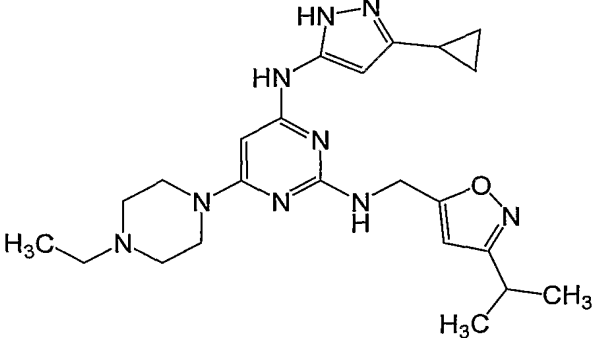
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| 630 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ⁶ -(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 631 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 632 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 633 |  | N ⁴ -bicyclo[2.2.1]hept-2-yl-N ⁶ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |
| 634 |  | N ⁴ -bicyclo[2.2.1]hept-2-yl-N ⁶ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 635 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]-6-[(1R,4R)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine |

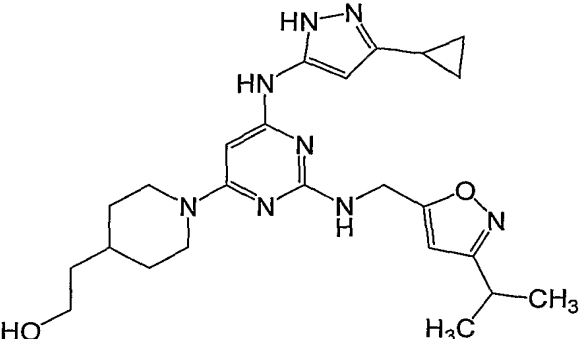
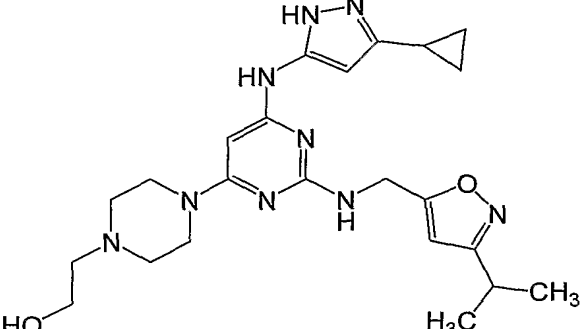
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| 636 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1R,4R)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine |
| 637 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-morpholin-4-yl- N^2 -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 638 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(dimethylamino)ethoxy]}- N^2 -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 639 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(5-fluoropyridin-2-yl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine |
| 640 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -{[3-(2-thienyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |

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| 641 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{{2-(dimethylamino)ethyl}oxy}- N^2 -[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 642 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)- N^2 -[(3-pyrimidin-5-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 643 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-morpholin-4-yl- N^2 -[(3-pyrimidin-5-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 644 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{{2-(diethylamino)ethyl}oxy}- N^2 -{{[3-(1-methylethyl)isoxazol-5-yl]methyl}}pyrimidine-2,4-diamine |
| 645 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{{[3-(1-methylethyl)isoxazol-5-yl]methyl}}-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |

| | | |
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| 646 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(diethylamino)ethyl]oxy}- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 647 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 648 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -{[3-(1,3-thiazol-2-yl)isoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 649 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-[2-(dimethylamino)ethoxy]- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 650 |  | 6-{[2-(dimethylamino)ethyl]oxy}- N^2 -[(3-methylisoxazol-5-yl)methyl]- N^4 -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |

| | | |
|-----|--|--|
| 651 | | 6-{[2-(diethylamino)ethyl]oxy}-N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |
| 652 | | N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 653 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl-N ² -[2-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine |
| 654 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl-N ² -[1-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine |
| 655 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 656 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine |

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| 657 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-{{2-(dimethylamino)ethyl}oxy}-N ² -[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 658 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-{{2-(diethylamino)ethyl}oxy}-N ² -[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 659 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-{{2-(pyrrolidin-1-ylethyl)oxy}pyrimidine-2,4-diamine |
| 660 |  | N ² -{{3-[(2-aminopyrimidin-4-yl)isoxazol-5-yl]methyl}-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 661 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-ethylpiperazin-1-yl)-N ² -{{3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |

| | | |
|-----|---|---|
| 662 |  | 2-(1-{6-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperidin-4-yl)ethanol |
| 663 |  | 2-(4-{6-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperazin-1-yl)ethanol |

[0084] Another aspect of the invention is a pharmaceutical composition comprising a compound according to any of formulas I-V or a compound as depicted in Table 1, and a pharmaceutically acceptable carrier.

[0085] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any of formulas I-V or a compound as depicted in Table 1.

[0086] Another aspect of the invention is a method of modulating the *in vivo* activity of IGF1R, the method comprising administering to a subject an effective IGF1R-modulating amount of a compound of any of formulas I-V or a compound as depicted in Table 1, or a pharmaceutical composition thereof.

[0087] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities effect directly or indirectly by IGF1R, the method comprising administering to a mammal (preferably human) in need thereof a therapeutically effective amount of a compound of any of formulas I-V or a compound as depicted in Table 1, or a pharmaceutical composition thereof.

[0088] Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of either a composition



comprising a compound of any of formulas I-V or a compound as depicted in Table 1, to a cell or a plurality of cells.

[0089] Another aspect of the invention is a method of inhibiting wild-type Abl, including the T315I Abl mutant, the method comprising administering an effective amount of either a composition comprising a compound of any of formulas I-V or a compound as depicted in Table 1, to a cell or a plurality of cells.

[0090] Another aspect of the invention is a method of treating diseases or disorders in a mammal, preferably a human, having a mutant-Abl malignancy, the method comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of any of formulas I-V or a compound as depicted in Table 1, or a pharmaceutical composition thereof.

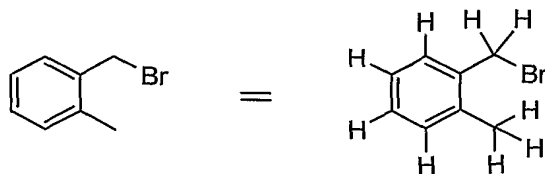
Definitions

[0091] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

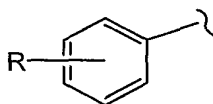
[0092] The symbol “-” means a single bond, “=” means a double bond, “≡” means a triple bond, “—” means a single or double bond. The symbol “” refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, E- or Z-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the “” symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[0093] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, -CH₂CH₂-. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques

are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

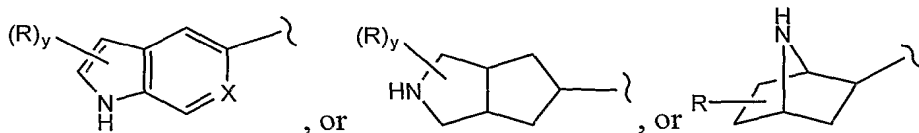


[0094] If a group “R” is depicted as “floating” on a ring system, as for example in the formula:



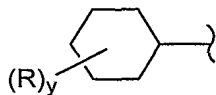
then, unless otherwise defined, a substituent “R” may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0095] If a group “R” is depicted as floating on a fused ring system, as for example in the formulae:

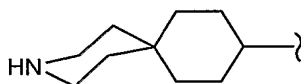


then, unless otherwise defined, a substituent “R” may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, “X” equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the “R” group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two “R”s may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0096] When a group “R” is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, “y” can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two “R’s” may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an “annular” carbon). In another example, two R’s on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a “spirocyclic” group) structure with the depicted ring as for example in the formula:



[0097] “Alkyl” is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, “C₈ alkyl” may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more than eight carbon atoms. A “C₀” alkyl (as in “C₀-C₆alkyl”) is a covalent bond. Exemplary alkyl groups are those of C₂₀ or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include *c*-propyl, *c*-butyl, *c*-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, either “butyl” or “C₄ alkyl” is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-ynyl groups; and for example, “propyl” or “C₃ alkyl” each include *n*-propyl, propenyl, and isopropyl.

[0098] “Alkylene” refers to straight or branched chain divalent group consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment

and, specifically, fully saturated. Examples of alkylene include ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), dimethylpropylene ($-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$), and cyclohexylpropylene ($-\text{CH}_2\text{CH}_2\text{CH}(\text{C}_6\text{H}_{13})$).

[0099] “Alkylidene” refers to a straight or branched chain unsaturated divalent group consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[00100] “Alkylidyne” refers to a straight or branched chain unsaturated divalent group consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0100] Any of the above groups, “alkylene,” “alkylidene” and “alkylidyne,” when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl group with a vinyl substituent at the 2-position of said group.

[0101] “Alkoxy” or “alkoxyl” refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0102] “Substituted alkoxy” refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is “polyalkoxy” or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, and glycol ethers such as polyethyleneglycol and $-\text{O}(\text{CH}_2\text{CH}_2\text{O})_x\text{CH}_3$, where *x* is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-\text{OCH}_2(\text{CH}_2)_y\text{OH}$, where *y* is for example an integer of between

about one and about ten, in another example y is an integer of between about one and about four.

[0103] “Acyl” refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0104] “ α -Amino Acids” refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α -amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, ornithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A “side chain of an α -amino acid” refers to the group found on the α -carbon of an α -amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

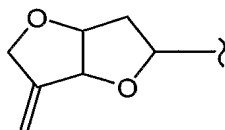
[0105] “Amino” refers to the group -NH_2 . “Substituted amino,” refers to the group -N(H)R or -N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0106] “Aryl” refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent substituents. As univalent substituents, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0107] “Arylene” generically refers to any aryl that has at least two groups attached thereto. For a more specific example, “phenylene” refers to a divalent phenyl ring group. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0108] “Arylalkyl” refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne group. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl and the corresponding alkylene, alkylidene, or alkylidyne group portion of an arylalkyl group may be optionally substituted. “Lower arylalkyl” refers to an arylalkyl where the “alkyl” portion of the group has one to six carbons; this can also be referred to as C₁₋₆ arylalkyl.

[0109] “Exo-alkenyl” refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0110] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (*i.e.* saturated ring structures) can contain two substitution groups.

[0111] “Fused-polycyclic” or “fused ring system” refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0112] “Halogen” or “halo” refers to fluorine, chlorine, bromine or iodine. “Haloalkyl” and “haloaryl” refer generically to alkyl and aryl groups that are substituted with one or more halogens, respectively. Thus, “dihaloaryl,” “dihaloalkyl,” “trihaloaryl” etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0113] “Heteroarylene” generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, “pyridylene” refers to a divalent pyridyl ring

group. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0114] "Heteroatom" refers to O, S, N, or P.

[0115] "Heterocyclyl" refers to a stable three- to fifteen-membered ring substituent that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl substituent may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl group may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to $-S-$ (sulfide), $-S(O)-$ (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring substituent may be partially or fully saturated or aromatic. Examples of heterocyclyl groups include, but are not limited to, azetidiny, acridiny, benzodioxoly, benzodioxany, benzofurany, carbazoy, cinnoliny, dioxolany, indoliziny, naphthyridiny, perhydroazepiny, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pteridiny, puriny, quinazoliny, quinoxaliny, quinoliny, isoquinoliny, tetrazoy, tetrahydroisoquinoly, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, azepiny, pyrroly, 4-piperidony, pyrrolidiny, pyrazoly, pyrazolidiny, imidazoly, imidazoliny, imidazolidiny, dihydropyridiny, tetrahydropyridiny, pyridiny, pyraziny, pyrimidiny, pyridaziny, oxazoly, oxazoliny, oxazolidiny, triazoly, isoxazoly, isoxazolidiny, morpholiny, thiazoly, thiazoliny, thiazolidiny, isothiazoly, quinuclidiny, isothiazolidiny, indoly, isoindoly, indoliny, isoindoliny, octahydroindoly, octahydroisoindoly, quinoly, isoquinoly, decahydroisoquinoly, benzimidazolyl, thiadiazolyl, benzopyrany, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyrany, thienyl, benzothienyl, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, dioxaphospholany, and oxadiazolyl.

[0116] “Heteroalicyclic” refers specifically to a non-aromatic heterocyclyl group. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0117] “Heteroaryl” refers specifically to an aromatic heterocyclyl group.

[0118] “Heterocyclylalkyl” refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne group. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl and the corresponding alkylene, alkylidene, or alkylidyne portion of a heterocyclylalkyl group may be optionally substituted. “Lower heterocyclylalkyl” refers to a heterocyclylalkyl where the “alkyl” portion of the group has one to six carbons. “Heteroalicycylalkyl” refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and “heteroarylalkyl” refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic. Such terms may be described in more than one way, for example, “lower heterocyclylalkyl” and “heterocyclyl C₁₋₆alkyl” are equivalent terms. Additionally, for simplicity, the number of annular atoms (including heteroatoms) in a heterocycle may be denoted as “C_x-C_y” (as in “C_x-C_y-heterocyclyl” and “C_x-C_y-heteroaryl” (and the like)), where x and y are integers. So, for example, C₅-C₁₄-heterocyclyl refers to a 5 to 14 membered ring system having at least one heteroatom and not a ring system containing 5 to 14 annular carbon atoms.

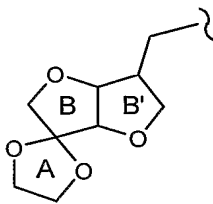
[0119] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, pyridotriazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolynyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolynyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizynyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl,

pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0120] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that with respect to any molecule described as containing one or more optional substituents, only sterically practical and/or synthetically feasible compounds are meant to be included. “Optionally substituted” refers to all subsequent modifiers in a term, for example in the term “optionally substituted arylC₁₋₈ alkyl,” optional substitution may occur on both the “C₁₋₈ alkyl” portion and the “aryl” portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitutions is presented below in the definition of “substituted.”

[0121] “Saturated bridged ring system” refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class “saturated bridged ring system.”

[0122] “Spirocyclyl” or “spirocyclic ring” refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B’), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0123] “Substituted” alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl), optionally substituted aryl (for example, 4-hydroxyphenyl), optionally substituted arylalkyl (for example, 1-phenyl-ethyl), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl or 1-methyl-piperidin-4-yl), optionally substituted alkoxy, alkylenedioxy (for example methylenedioxy), optionally substituted amino (for example, alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy), optionally substituted arylalkyloxy (for example, benzyloxy), carboxy ($-\text{CO}_2\text{H}$), carboalkoxy (that is, acyloxy or $-\text{OC}(=\text{O})\text{R}$), carboxyalkyl (that is, esters or $-\text{CO}_2\text{R}$), carboxamido, benzyloxycarbonylamino (CBZ-amino), cyano, acyl, halogen, hydroxy, nitro, sulfanyl, sulfinyl, sulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, acylamino, and sulfonamido.

[0124] “Sulfanyl” refers to the groups: $-\text{S}$ -(optionally substituted alkyl), $-\text{S}$ -(optionally substituted aryl), and $-\text{S}$ -(optionally substituted heterocyclyl).

[0125] “Sulfinyl” refers to the groups: $-\text{S}(\text{O})-\text{H}$, $-\text{S}(\text{O})$ -(optionally substituted alkyl), $-\text{S}(\text{O})$ -(optionally substituted aryl), and $-\text{S}(\text{O})$ -(optionally substituted heterocyclyl).

[0126] “Sulfonyl” refers to the groups: $-\text{S}(\text{O}_2)-\text{H}$, $-\text{S}(\text{O}_2)$ -(optionally substituted alkyl), $-\text{S}(\text{O}_2)$ -(optionally substituted aryl), $-\text{S}(\text{O}_2)$ -(optionally substituted heterocyclyl), $-\text{S}(\text{O}_2)$ -(optionally substituted alkoxy), $-\text{S}(\text{O}_2)$ -(optionally substituted aryloxy), and $-\text{S}(\text{O}_2)$ -(optionally substituted heterocycliloxy).

[0127] “Yield” for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0128] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is

understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, *i.e.*, amino, imino, hydroxy or oxo, respectively.

[0129] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0130] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0131] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0132] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0133] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent group, for example, -OCH₂-, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent groups are not to be construed as limited to the depicted orientation, for example “-OCH₂-” is meant to mean not only “-OCH₂-” as drawn, but also “-CH₂O-.”

[0134] In addition to the preferred embodiments recited hereinabove, also preferred are embodiments comprising combinations of preferred embodiments.

[0135] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or

chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0136] “Patient” for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0137] “Kinase-dependent diseases or conditions” refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0138] While not wishing to be bound to theory, phosphatases can also play a role in “kinase-dependent diseases or conditions” as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore

compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (*i.e.* tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0139] “Therapeutically effective amount” is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a “therapeutically effective amount” will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[0140] “Cancer” refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma,

chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0141] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0142] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron,

zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0143] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0144] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example,

biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0145] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0146] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0147] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, *i.e.*, arresting its development; and (iii) relieving the disease-state, *i.e.*, causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0148] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular IRK, IGF1R, c-Met, c-Kit, KDR, flt-3, or flt-4-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the

shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0149] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (*e.g.* as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0150] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0151] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting

operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0152] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0153] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0154] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

[0155] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water,

ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0156] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0157] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0158] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0159] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a

pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0160] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0161] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0162] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0163] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0164] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed.,

(Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0165] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

Utility of compounds of the invention as screening agents

[0166] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example IGF1R, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0167] The determination of the binding of the candidate agent to, for example, IGF1R may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding

determined directly. For example, this may be done by attaching all or a portion of the IGF1R protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0168] The term “labeled” as used herein is meant to include both direct and indirect labeling with a compound that provides a detectable signal, for example, radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin, and the like. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0169] In some embodiments, only one of the components is labeled. For example, IGF1R protein may be labeled at tyrosine positions using ^{125}I , or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophore for the candidate agents.

[0170] The compounds of the invention may also be used as competitors to screen for additional drug candidates. The terms “candidate bioactive agent” or “drug candidate” or grammatical equivalents as used herein describe any molecule, *e.g.*, protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as “exogenous” agents. In one example, exogenous agents further exclude antibodies to IGF1R.

[0171] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 and less than about

2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0172] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0173] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to IGF1R, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0174] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to IGF1R protein for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C.

[0175] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0176] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to IGF1R and thus is capable of binding to, and potentially modulating, the activity of the IGF1R. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0177] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to IGF1R with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to IGF1R.

[0178] It may be of value to identify the binding site of IGF1R. This can be done in a variety of ways. In one embodiment, once IGF1R is identified as binding to the candidate agent, the IGF1R is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0179] Modulation is tested by screening for candidate agents capable of modulating the activity of IGF1R comprising the steps of combining a candidate agent with IGF1R, as above, and determining an alteration in the biological activity of the IGF1R. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

[0180] Alternatively, differential screening may be used to identify drug candidates that bind to native IGF1R, but cannot bind to modified IGF1R.

[0181] Positive controls and negative controls can be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a

radiolabel is employed, the samples can be counted in a scintillation counter to determine the amount of bound compound.

[0182] A variety of other reagents can be included in the screening assays. These include reagents like salts, neutral proteins, *e.g.*, albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components can be added in any order that provides for the requisite binding.

[0183] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular IGF1R -ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of IGF1R kinase's as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of IGF1R kinase's and in solving the structures of other proteins with similar features. Ligands of such complexes may include compounds of the invention as described herein.

[0184] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of IGF1R kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a IGF1R kinase in a conformation (*e.g.* as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0185] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for IGF1R kinase modulation, and determining whether said candidate agent modulates IGF1R kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate IGF1R kinase activity, to a mammal suffering from a condition treatable by IGF1R kinase modulation, such as those described above.

[0186] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a IGF1R kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a IGF1R kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the IGF1R kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

Abbreviations and their Definitions

[0187] The following abbreviations and terms have the indicated meanings throughout:

| Abbreviation | Meaning |
|---------------------|-----------------------------------|
| Ac | acetyl |
| ATP | adenosine triphosphate |
| BNB | 4-bromomethyl-3-nitrobenzoic acid |
| Boc | t-butyloxy carbonyl |
| br | broad |
| Bu | butyl |
| °C | degrees Celsius |
| c- | cyclo |
| CBZ | CarboBenZoxy = benzyloxycarbonyl |
| d | doublet |
| dd | doublet of doublet |

| Abbreviation | Meaning |
|--------------|---|
| dt | doublet of triplet |
| DBU | Diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane = methylene chloride = CH_2Cl_2 |
| DCE | Dichloroethylene |
| DEAD | diethyl azodicarboxylate |
| DIC | Diisopropylcarbodiimide |
| DIEA | N,N-diisopropylethyl amine |
| DMAP | 4-N,N-dimethylaminopyridine |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DVB | 1,4-divinylbenzene |
| EEDQ | 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline |
| EI | Electron Impact ionization |
| Et | Ethyl |
| Fmoc | 9-fluorenylmethoxycarbonyl |
| g | gram(s) |
| GC | gas chromatography |
| h or hr | hour(s) |
| HATU | 0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HMDS | Hexamethyldisilazane |
| HOAc | acetic acid |
| HOBt | Hydroxybenzotriazole |
| HPLC | high pressure liquid chromatography |
| L | liter(s) |
| M | molar or molarity |
| m | Multiplet |
| Me | Methyl |
| mesyl | Methanesulfonyl |

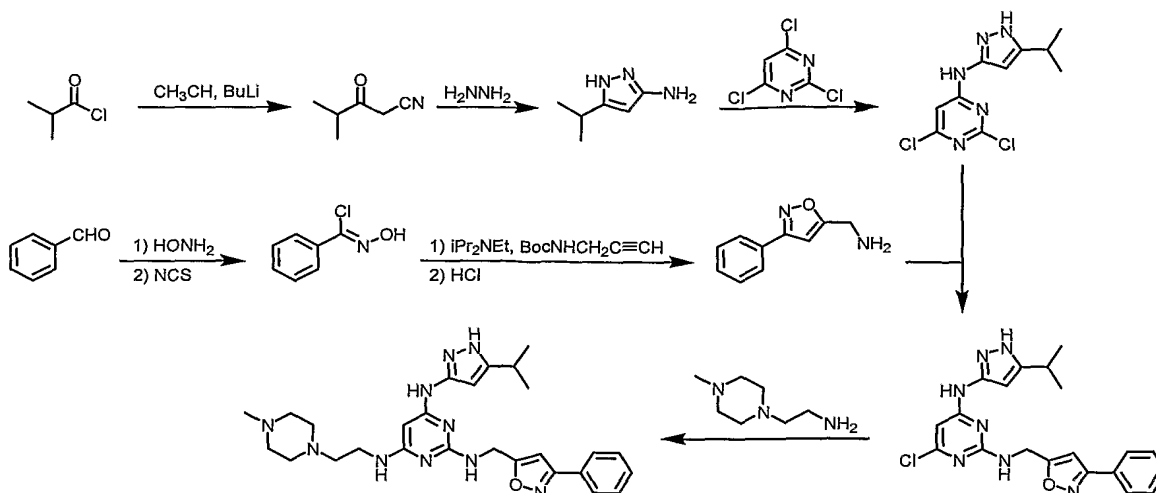
| Abbreviation | Meaning |
|---------------------|---|
| mg | milligram(s) |
| MHz | megahertz (frequency) |
| Min | minute(s) |
| mL | milliliter(s) |
| mM | Millimolar |
| mmol | millimole(s) |
| mol | mole(s) |
| MS | mass spectral analysis |
| MTBE | methyl t-butyl ether |
| N | normal or normality |
| NBS | N-bromosuccinimide |
| NCS | N-chlorosuccinimide |
| nM | Nanomolar |
| NMO | N-methylmorpholine oxide |
| NMR | nuclear magnetic resonance spectroscopy |
| PEG | polyethylene glycol |
| pEY | poly-glutamine, tyrosine |
| Ph | Phenyl |
| PhOH | Phenol |
| PfP | Pentafluorophenol |
| PfPy | Pentafluoropyridine |
| PPTS | Pyridinium p-toluenesulfonate |
| Py | Pyridine |
| PyBroP | bromo-tris-pyrrolidino-phosphonium hexafluorophosphate |
| q | Quartet |
| RT | Room temperature |
| Sat'd | Saturated |
| s | Singlet |

| Abbreviation | Meaning |
|--------------|----------------------------|
| s- | Secondary |
| t- | Tertiary |
| t or tr | Triplet |
| TBDMS | t-butyldimethylsilyl |
| TES | Triethylsilyl |
| TFA | trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TMOF | trimethyl orthoformate |
| TMS | trimethylsilyl |
| tosyl | p-toluenesulfonyl |
| Trt | triphenylmethyl |
| uL | microliter(s) |
| uM | Micromole(s) or micromolar |

Examples

[0188] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, but not necessarily, each example set out below describes a multi-step synthesis as outlined above.

[0189] **EXAMPLE 1.** N⁴-(5-Isopropyl-1H-pyrazol-3-yl)-N⁶-[2-(4-methylpiperazin-1-yl)ethyl]-N²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4,6-triamine



[0190] 4-Methyl-3-oxopentanenitrile. A solution of acetonitrile (25.2 mL, 480 mmol) in THF (300 mL) was cooled to -78°C in a dry ice/acetone bath, and *n*-butyllithium (255 mL, 1.6 M in hexanes, 408 mmol) was added dropwise. The solution was stirred at -78°C for 2 h and isobutyryl chloride (25.2 mL, 240 mmol) was added dropwise. The reaction was maintained at -78°C for 1 h, allowed to warm to room temperature for 2 h and then stored in a refrigerator overnight. The reaction was quenched with 3 N HCl, extracted with ether, washed with water and brine and dried over sodium sulfate. The solvent was removed on a rotary evaporator to give the desired product (25 g, 94%) as a light brown oil that was used without further purification.

[0191] 5-Isopropyl-1H-pyrazol-3-ylamine. A solution of 4-methyl-3-oxopentanenitrile (25 g, 225 mmol) and hydrazine (6.75 mL, 215 mmol) in ethanol (250 mL) was stirred at room temperature for 3 h, at which point LC/MS indicated exclusively product remained. The mixture was concentrated on a rotary evaporator followed by under high vacuum to give the desired product (27.8 g, 99 %) as a yellow semisolid that was used without further purification.

[0192] 2,6-Dichloropyrimidin-4-yl-(5-isopropyl-1H-pyrazol-3-yl)-amine. A mixture of 2,4,6-trichloropyrimidine (1.8 g, 9.8 mmol), 5-isopropyl-1H-pyrazol-3-ylamine (1.25 g, 10.0 mmol), diisopropylethylamine (3 mL, 18 mmol) and 1-butanol (10 mL) was heated to 80°C for 2 h, at which point LC/MS indicated that the reaction was complete. The solvents were removed on a rotary evaporator and the paste was treated with ethyl acetate. The organic solution was washed with water and brine and dried over magnesium sulfate. The

residue was concentrated on a rotary evaporator, and the pale yellow solid that remained was purified via flash chromatography to yield the desired product (2.3 g, 70 %) as an off white solid.

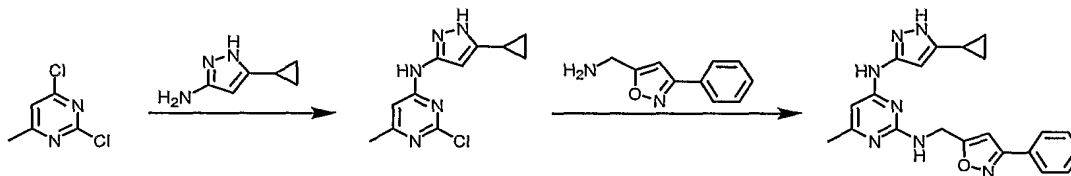
[0193] 3-Phenylisoxazol-5-ylmethanamine. A solution of 20% (w/v) sodium hydroxide (100 mL) was cooled to 0 °C and a solution of hydroxylamine hydrochloride (39.3 g, 565 mmol) in water (80 mL) was added. The mixture was stirred at 0 °C for 20 min and a solution of benzaldehyde (50.0 g, 471 mmol) was added such that the temperature was maintained below 0 °C. The cold reaction was stirred for an additional 2 h and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give 56.4 g (99 %) of a yellow oil. This residue was taken up in dichloromethane (1 L) containing DMF (20 mL) and cooled to 0 °C in an ice bath. N-Chlorosuccinimide (62.2 g, 466 mmol) was added slowly such that the temperature was maintained at 0 °C until addition was complete, then the reaction was allowed to warm to room temperature for 2 h. The mixture was stirred with water (500 mL) for 15 min, then the layers separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed with water, 10% lithium chloride and brine, then dried over sodium sulfate. The solvent was removed on a rotary evaporator to give a yellow oil (64.5 g, 89 %) that was dissolved in THF (300 mL). This solution was added dropwise to a solution of *N*-Boc-propargylamine (53.8 g, 347 mmol) in THF (1 L) that had been cooled to 0 °C. Upon completion of addition, the solution was allowed to warm to room temperature and stirred overnight. The solution was concentrated on a rotary evaporator and taken up in dichloromethane (500 mL). The organic solution was washed with water and brine, dried over sodium sulfate and concentrated on a rotary evaporator to give a yellow oil that was taken up in 4N HCl in dioxane (500 mL). The mixture was stirred at room temperature and over time formed a white suspension. The suspension was diluted with dichloromethane (2 L) and stirred at room temperature overnight. The solid that had formed was collected by filtration, dissolved in methanol and made basic with 2N sodium hydroxide. The basic solution was extracted with ethyl acetate and the organic layers were dried over sodium sulfate and concentrated on a rotary evaporator to give a yellow oil that solidified overnight. The solid was stirred with hexanes, then filtered, washed with hexanes and dried to give the desired product (44.5 g, 74 %) as a light yellow solid.

[0194] **6-Chloro-*N*⁴-(5-isopropyl-1*H*-pyrazol-3-yl)-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine.** To a solution of 2,6-dichloropyrimidin-4-yl-(5-isopropyl-1*H*-pyrazol-3-yl)-amine (19.44 g, 71.7 mmol) in 1-butanol (200 mL) was added diisopropylethylamine (23.7 mL, 143 mmol) and 3-phenylisoxazol-5-ylmethylamine (15.0 g, 86.1 mmol). The mixture was stirred at 90 °C for 30 h, then concentrated on a rotary evaporator. The residue was taken up in 100 mL of methanol and boiled until the volume reached around 50 mL. The solution was allowed to cool to room temperature and then placed in the refrigerator overnight. The solid that formed was collected by filtration, while the filtrate was concentrated on a rotary evaporator, heated to boiling in methanol and cooled overnight in the refrigerator. This solid was collected and the filtrate was subjected to methanol recrystallization a third time. The three solids were combined to give the desired product (13.1 g, 45 %) as a white solid.

[0195] ***N*⁴-(5-Isopropyl-1*H*-pyrazol-3-yl)-*N*⁶-[2-(4-methylpiperazin-1-yl)ethyl]-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4,6-triamine.** A mixture of 6-chloro-*N*⁴-(5-isopropyl-1*H*-pyrazol-3-yl)-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine (250 mg, 0.611 mmol) and 2-(4-methylpiperazin-1-yl)-ethylamine (500 mg, 3.50 mmol) in 1-butanol (2 mL) was heated to 180 °C in a 50 mL sealed tube. The mixture was heated for 1 h, then cooled to room temperature and diluted with methanol (10 mL). The mixture thus obtained was purified via preparative reverse phase HPLC to give the desired product (93 mg, 29 %) as a white solid.

[0196] ¹H-NMR (400MHz, d₆-CDCl₃): δ 7.8 (m, 2H), 7.4 (m, 3H), 6.5 (s, 1H), 5.9 (s, 1H), 5.2 (s, 1H), 4.8 (m, 2H), 3.5 (br s, 2H), 2.8 (m, 1H), 2.5 (m, 10H), 2.4 (s, 3H), 1.2 (m, 6H); MS (EI) for C₂₇H₃₆N₁₀O: 517.3 (MH⁺).

EXAMPLE 2. *N*⁴-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-6-methyl-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4,6-triamine

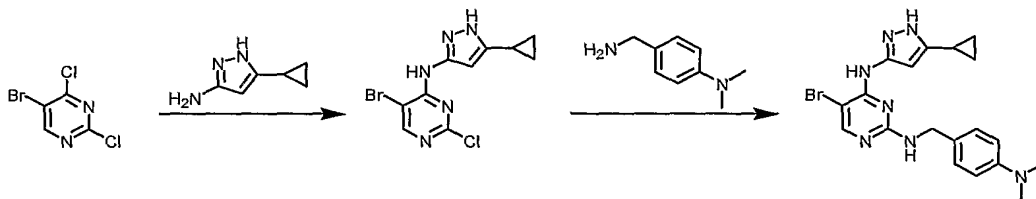


[0197] **2-Chloro-6-methylpyrimidin-4-yl-(5-cyclopropyl-1H-pyrazol-3-yl)-amine.** A mixture of 2,4-dichloro-6-methylpyrimidine (30.0 g, 184 mmol), 5-cyclopropyl-1H-pyrazol-3-ylamine (22.6 g, 184 mmol) and diisopropylethylamine (46 mL, 278 mmol) in 1-butanol (50 mL) was heated to 60 °C for 65 h. The reaction was cooled to room temperature and diluted with ethyl acetate. The mixture was washed with 2 N sodium hydroxide, water and brine, then dried over sodium sulfate and concentrated on a rotary evaporator. The residue was treated with a small amount of acetonitrile, sonicated and then triturated with ether until a solid was formed. The solid was collected by filtration to give the desired product (23.0 g, 50 %) as a yellow solid.

[0198] ***N*⁴-(5-Cyclopropyl-1H-pyrazol-3-yl)-6-methyl-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4,6-triamine.** A mixture of 2-chloro-6-methylpyrimidin-4-yl-(5-cyclopropyl-1H-pyrazol-3-yl)-amine (1.9 g, 7.6 mmol), 3-phenylisoxazol-5-ylmethylamine (1.7 g, 9.9 mmol) and diisopropylethylamine (1.8 mL, 11 mmol) in 1-butanol (30 mL) was heated to 160 °C in a 50 mL sealed tube for 8 h. The hot mixture was filtered to give the desired product (1.7 g, 58 %) as a white solid.

[0199] ¹H-NMR (400MHz, d₆-DMSO): δ 11.8 (s, 1H), 9.2 (s, 1H), 7.8 (d, 2H), 7.45 (t, 3H), 7.25 (br s, 1H), 6.75 (s, 1H), 6.2 (br s, 1H), 4.65 (d, 2H), 2.1 (s, 3H), 1.8 (m, 1H), 0.9 (br d, 2H), 0.6 (br s, 2H); MS (EI) for C₂₁H₂₁N₇O: 388.5 (MH⁺).

[0200] **EXAMPLE 3. 5-Bromo-*N*⁴-(5-cyclopropyl-1H-pyrazol-3-yl)-*N*²-(4-dimethylaminobenzyl)-pyrimidine-2,4-diamine.**

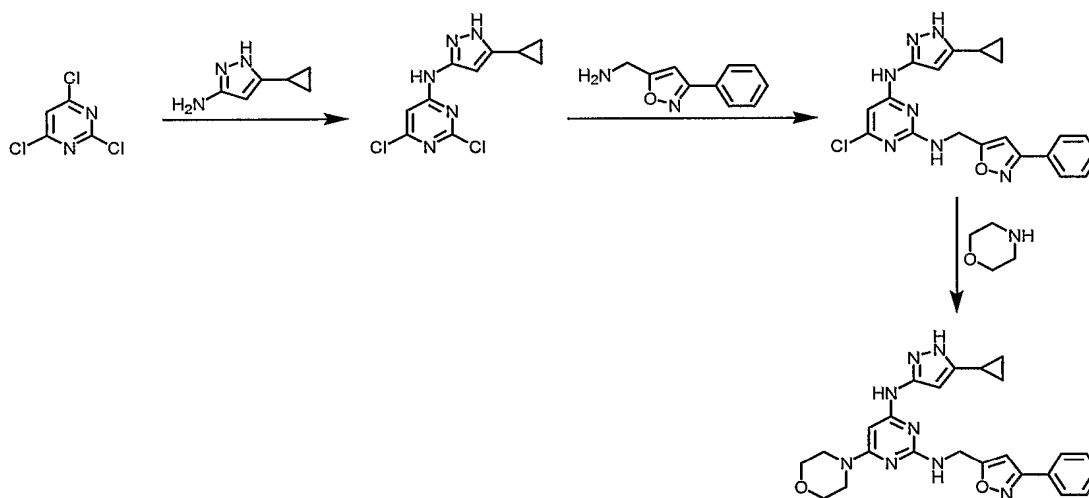


[0201] **5-Bromo-2-chloropyrimidin-4-yl-(5-cyclopropyl-1H-pyrazol-3-yl)-amine.** A mixture of 5-bromo-2,4-dichloropyrimidine (15.4 g, 67.6 mmol), 5-cyclopropyl-1H-pyrazol-3-ylamine (10.0 g, 81.3 mmol) and diisopropylethylamine (17 mL, 102 mmol) in 1-butanol (150 mL) was heated to 80 °C for 1 h. The solid that formed was collected by filtration and washed with acetonitrile to give the desired product (15.8 g, 75 %) as a white solid.

[0202] 5-Bromo-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(4-dimethylaminobenzyl)-pyrimidine-2,4-diamine. A mixture of 5-bromo-2-chloropyrimidin-4-yl-(5-cyclopropyl-1*H*-pyrazol-3-yl)-amine (313 mg, 1.00 mmol) and 4-dimethylaminobenzylamine (225 mg, 1.5 mmol) in 1-butanol (20 mL) was heated to 170 °C in a 50 mL sealed tube for 3 h. The mixture was cooled and diluted with ethyl acetate. The organic layer was washed with 2 N sodium hydroxide, water and brine and dried over sodium sulfate. The solution was concentrated, redissolved in DMF and purified by preparative reverse phase HPLC to give the desired product (124 mg, 29 %) as a white solid.

[0203] ¹H-NMR (400MHz, d₆-DMSO): δ 12.1 (s, 1H), 8.0 (br s, 1H), 7.2 (d, 2H), 6.6 (d, 2H), 4.4 (d, 2H), 2.8 (s, 6H), 1.8 (s, 1H), 1.0-0.6 (m, 4H); MS (EI) for C₁₉H₂₂N₇Br: 430.3 (MH⁺).

[0204] EXAMPLE 4. *N*⁴-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-6-morpholin-4-yl-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine



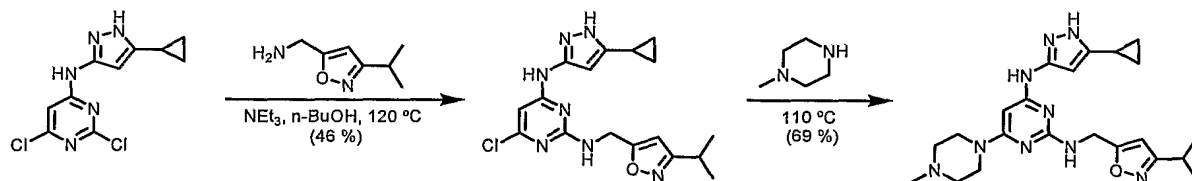
[0205] 2,6-Dichloropyrimidin-4-yl-(5-cyclopropyl-1*H*-pyrazol-3-yl)-amine. A mixture of 2,4,6-trichloropyrimidine (30 g, 163 mmol), 5-cyclopropyl-1*H*-pyrazol-3-ylamine (20 g, 163 mmol), diisopropylethylamine (50 mL, 300 mmol) and 1-butanol (100 mL) was heated to 80 °C for 2 h. The solvents were removed on a rotary evaporator and the residue was taken up in ethyl acetate. The organic solution was washed with water and brine and dried over magnesium sulfate. The residue was concentrated on a rotary evaporator to give the desired product (40.7 g, 92 %) as a light yellow solid.

[0206] 6-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine. To a solution of 2,6-dichloropyrimidin-4-yl-(5-cyclopropyl-1*H*-pyrazol-3-yl)-amine (19.3 g, 71.7 mmol) in 1-butanol (200 mL) was added diisopropylethylamine (23.7 mL, 143 mmol) and 3-phenylisoxazol-5-ylmethylamine (15.0 g, 86.1 mmol). The mixture was stirred at 90 °C for 30 h, then concentrated on a rotary evaporator. The residue was taken up in 100 mL of methanol and boiled until the volume reached around 50 mL. The solution was allowed to cool to room temperature and then placed in the refrigerator overnight. The solid that formed was collected by filtration, while the filtrate was dissolved in dichloromethane and sonicated. The solid that formed was collected and combined with the first recrystallized crop to give the desired product (17.8 g, 61 %) as a white solid.

[0207] *N*⁴-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-6-morpholin-4-yl-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine. A mixture of 6-chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(3-phenylisoxazol-5-ylmethyl)-pyrimidine-2,4-diamine (8.0 g, 19.7 mmol) and morpholine (5.0 g, 57.4 mmol) was heated to 100 °C for 4h, then concentrated on a rotary evaporator and treated with a minimal amount of methanol. The mixture was sonicated until a precipitate began to form, then water was added and the mixture was sonicated again. The solid that had formed was collected by filtration and washed with ether to give a white solid that was contaminated with excess morpholine. The solid was stirred overnight with 3 N HCl, then filtered and lyophilized to give the HCl salt of the desired product (9.3 g, 96 %) as a white solid.

[0208] ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.78 (m, 2H), 7.45 (m, 3H), 6.51 (s, 1H), 5.95 (br s, 0.3H), 5.68 (br s, 0.2H), 4.68 (s, 2H), 3.68 (t, 4H), 3.46 (t, 4H), 1.85 (m, 1H), 0.91 (br s, 2H), 0.69 (br s, 2H); MS (EI) for C₂₄H₂₆N₈O₂: 459 (MH⁺).

[0209] EXAMPLE 5. *N*⁴-(5-Cyclopropyl-2*H*-pyrazol-3-yl)-*N*²-(3-isopropyl-isoxazol-5-ylmethyl)-6-(4-methyl-piperazin-1-yl)-pyrimidine-2,4-diamine



6-Chloro-*N*⁴-(5-cyclopropyl-2*H*-pyrazol-3-yl)-*N*²-(3-isopropyl-isoxazol-5-ylmethyl)-pyrimidine-2,4-diamine. A mixture of 2,6-dichloropyrimidin-4-yl-(5-cyclopropyl-1*H*-

pyrazol-3-yl)-amine (73.6 g, 274 mmol), 5-isopropyl-1*H*-pyrazol-3-ylamine (46.0 g, 329 mmol) and triethylamine (76.3 mL, 548 mmol) in *n*-butanol (1 L) was heated to 120 °C and monitored by LCMS. The reaction was complete after 16 h, at which point it was cooled to room temperature and diluted with ethyl acetate. The mixture was washed with *N* sodium hydroxide, water and brine, then dried over sodium sulfate and concentrated on a rotary evaporator. The residue was treated with ethyl acetate, heated to boiling and the yellow solid was collected via hot filtration and purified via recrystallization from methanol/ethyl acetate to give the product (37.7 g) as a white solid. The mother liquor was concentrated on a rotary evaporator, treated with ethyl acetate, heated to boiling and sonicated to give an additional 9.0 g of the product (46 % overall yield).

[0210] *N*⁴-(5-Cyclopropyl-2*H*-pyrazol-3-yl)-*N*²-(3-isopropyl-isoxazol-5-ylmethyl)-6-(4-methyl-piperazin-1-yl)-pyrimidine-2,4-diamine. A mixture of 6-chloro-*N*⁴-(5-cyclopropyl-2*H*-pyrazol-3-yl)-*N*²-(3-isopropyl-isoxazol-5-ylmethyl)-pyrimidine-2,4-diamine (45.5 g, 122 mmol) and 1-methylpiperazine (150 mL, 135 mmol) was heated to 110 °C for 3 h, at which time LC/MS indicated the reaction was complete. The mixture was diluted with methanol and ethyl acetate, then washed with aqueous 2 *N* sodium hydroxide, water, and brine. The combined organics were dried over sodium sulfate and concentrated on a rotary evaporator. The solid was treated with methanol, heated to boiling and allowed to cool to room temperature overnight. Collection of the precipitate via filtration gave the product (38.9 g) as a white solid. The mother liquor was concentrated on a rotary evaporator, diluted with methanol, heated to boiling and allowed to cool to room temperature overnight to afford a second crop (9.0 g, 90 % overall yield) of the product as a white solid. The material obtained in this fashion was 98 % pure by analytical HPLC. This material was then purified using preparative HPLC. The fractions that contained pure product were combined, diluted with ethyl acetate and washed with aqueous 2 *N* sodium hydroxide and brine and dried over sodium sulfate. Concentration on a rotary evaporator gave the product (36.7 g, 69 %) as a white solid that was > 99 % pure by analytical HPLC.

[0211] ¹H NMR (400 MHz, *d*₆-DMSO): δ 11.20 (s, 1H), 6.42 (s, 1H), 5.80 (s, 1H), 5.73 (s, 1H), 4.66 (d, *J* = 5.6, 2H), 4.34 (m, 2H), 3.40 (m, 4H), 3.02 (m, 2H), 2.97 (m, 1H), 2.77 (s, 3H), 1.93 (m, 1H), 1.20 (d, *J* = 7.2, 6H), 0.97 (m, 2H), 0.73 (m, 2H). MS (EI) for C₂₂H₃₁N₉O•HCl: 438 (MH⁺).

Assays

[0212] Kinase assays were performed by measurement of incorporation of γ - ^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60 μl /well of 20 $\mu\text{g}/\text{ml}$ MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100 μl TBS. Kinase reactions were carried out in a total volume of 34 μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM MgCl_2 , 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ - ^{33}P ATP was added to start the reaction (2x10⁶ cpm of γ - ^{33}P ATP per well (3000Ci/mmol) and either 10 μM or 30 μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50 μl /well scintillation fluid (Wallac). Radioactivity was measured using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one of ordinary skill in the art.

[0213] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i . The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC_{50} 's of, for example, less than about 100 μM , less than about 10 μM , less than about 1 μM , and further for example having IC_{50} 's of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (*i.e.*, there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (*i.e.*, compound concentration) data are fitted to equation (1) below; where V is the

observed rate, V_{\max} , is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

Equation (1)

$$V = V_{\max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

Kinase Specific Assays:

[0214] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to four-parameter equation (2) below; where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

Equation (2)

$$Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + (X/IC_{50})^H)$$

[0215] IGF1R kinase Assay

[0216] IGF1R kinase biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 3 μ M ATP, 4 μ M poly EY peptide and 4nM IGF1R (baculovirus expressed human IGF1R kinase domain residues M954-C1367) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM MgCl₂, 0.02% Triton X-100, 1mM DTT, 2mM MnCl₂). The mixture is incubated at ambient temperature for 2 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5

(or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μ M AMP, 28 μ g/mL luciferin and 40,000 units of light/mL luciferase.

[0217] Wild-type Abl assay

[0218] Kinase activity of wild-type Abl (ProQinase, Freiburg, Germany) and T315I Abl (Upstate, NY) is measured as the percent of ATP consumed following the kinase reaction using luciferase-luciferin-coupled chemiluminescence. Reactions were conducted in 384-well white, medium binding microtiter plates (Greiner). Kinase reactions were initiated by combining test compounds, ATP, poly(Glu, Tyr) and kinase in a 20 μ L volume (final concentrations: 1 μ M ATP, 2 μ M poly(Glu, Tyr), 10 nM wild-type Abl or 5 nM T315I Abl). The reaction mixture was incubated at ambient temperature for 2 h. Following the kinase reaction, a 20 μ L aliquot of luciferase-luciferin mix (Promega, Madison, WI) was added and the chemiluminescence signal measured using a Victor2 plate reader (Perkin Elmer).

Structure Activity Relationships

[0219] Tables 2 and 3 show structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC₅₀ with the following key: A = IC₅₀ less than 50 nM, B = IC₅₀ greater than 50 nM, but less than 500 nM, C = IC₅₀ greater than 500 nM, but less than 5000 nM, and D = IC₅₀ equal to or greater than 5,000 nM.

Table 2

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 1 | B | A |
| 2 | B | B |
| 3 | B | A |
| 4 | B | B |
| 5 | B | B |
| 6 | B | B |
| 7 | C | C |
| 8 | B | B |
| 9 | B | B |
| 10 | B | B |
| 11 | B | B |
| 12 | B | B |
| 13 | B | A |
| 14 | B | B |
| 15 | B | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 16 | B | C |
| 17 | B | A |
| 18 | B | B |
| 19 | C | C |
| 20 | C | B |
| 21 | B | C |
| 22 | C | B |
| 23 | B | A |
| 24 | B | A |
| 25 | B | C |
| 26 | B | A |
| 27 | B | B |
| 28 | B | B |
| 29 | C | B |
| 30 | C | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 31 | C | B |
| 32 | B | B |
| 33 | B | B |
| 34 | B | C |
| 35 | B | B |
| 36 | C | B |
| 37 | C | B |
| 38 | C | B |
| 39 | B | B |
| 40 | C | A |
| 41 | C | A |
| 42 | B | A |
| 43 | B | A |
| 44 | C | A |
| 45 | A | A |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 46 | A | A |
| 47 | C | A |
| 48 | C | A |
| 49 | B | A |
| 50 | C | A |
| 51 | D | A |
| 52 | C | A |
| 53 | B | A |
| 54 | B | A |
| 55 | B | A |
| 56 | C | A |
| 57 | C | A |
| 58 | C | A |
| 59 | B | A |
| 60 | C | A |
| 61 | B | A |
| 62 | B | A |
| 63 | B | A |
| 64 | B | A |
| 65 | C | A |
| 66 | B | A |
| 67 | C | A |
| 68 | C | A |
| 69 | C | A |
| 70 | B | B |
| 71 | B | B |
| 72 | C | B |
| 73 | B | B |
| 74 | C | B |
| 75 | B | B |
| 76 | B | B |
| 77 | C | B |
| 78 | C | B |
| 79 | C | B |
| 80 | B | B |
| 81 | C | B |
| 82 | B | B |
| 83 | B | B |
| 84 | B | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 85 | C | B |
| 86 | B | B |
| 87 | B | B |
| 88 | B | B |
| 89 | C | B |
| 90 | C | B |
| 91 | B | B |
| 92 | B | B |
| 93 | C | B |
| 94 | B | B |
| 95 | B | B |
| 96 | B | B |
| 97 | C | B |
| 98 | B | B |
| 99 | C | B |
| 100 | C | B |
| 101 | B | B |
| 102 | C | B |
| 103 | C | B |
| 104 | B | B |
| 105 | C | B |
| 106 | C | B |
| 107 | C | B |
| 108 | B | B |
| 109 | D | B |
| 110 | B | B |
| 111 | C | B |
| 112 | B | B |
| 113 | C | B |
| 114 | B | B |
| 115 | C | B |
| 116 | C | B |
| 117 | B | B |
| 118 | C | B |
| 119 | C | B |
| 120 | C | B |
| 121 | B | B |
| 122 | B | B |
| 123 | C | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 124 | C | B |
| 125 | B | B |
| 126 | C | B |
| 127 | C | B |
| 128 | C | B |
| 129 | C | B |
| 130 | B | B |
| 131 | C | B |
| 132 | B | B |
| 133 | C | B |
| 134 | C | B |
| 135 | C | B |
| 136 | B | B |
| 137 | B | B |
| 138 | B | B |
| 139 | B | B |
| 140 | C | B |
| 141 | C | B |
| 142 | C | B |
| 143 | C | B |
| 144 | C | B |
| 145 | C | B |
| 146 | C | B |
| 147 | C | B |
| 148 | B | B |
| 149 | C | B |
| 150 | B | B |
| 151 | C | B |
| 152 | C | B |
| 153 | D | B |
| 154 | D | B |
| 155 | C | B |
| 156 | C | B |
| 157 | C | C |
| 158 | C | C |
| 159 | C | C |
| 160 | D | C |
| 161 | C | C |
| 162 | C | C |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 163 | C | C |
| 164 | C | C |
| 165 | C | C |
| 166 | C | C |
| 167 | C | C |
| 168 | B | C |
| 169 | C | C |
| 170 | C | C |
| 171 | C | C |
| 172 | B | C |
| 173 | C | C |
| 174 | C | C |
| 175 | C | C |
| 176 | D | C |
| 177 | C | C |
| 178 | B | C |
| 179 | C | C |
| 180 | C | C |
| 181 | C | C |
| 182 | C | C |
| 183 | B | C |
| 184 | C | C |
| 185 | C | C |
| 186 | C | C |
| 187 | C | C |
| 188 | C | C |
| 189 | B | C |
| 190 | D | C |
| 191 | C | C |
| 192 | C | C |
| 193 | D | C |
| 194 | C | C |
| 195 | C | C |
| 196 | C | C |
| 197 | C | C |
| 198 | D | C |
| 199 | C | C |
| 200 | D | C |
| 201 | D | C |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 202 | C | C |
| 203 | C | C |
| 204 | C | C |
| 205 | C | C |
| 206 | C | C |
| 207 | C | C |
| 208 | D | C |
| 209 | C | C |
| 210 | B | C |
| 211 | C | C |
| 212 | C | C |
| 213 | C | C |
| 214 | D | C |
| 215 | D | C |
| 216 | C | C |
| 217 | C | C |
| 218 | C | C |
| 219 | C | C |
| 220 | B | C |
| 221 | C | C |
| 222 | C | C |
| 223 | B | C |
| 224 | C | C |
| 225 | C | C |
| 226 | D | C |
| 227 | C | C |
| 228 | C | C |
| 229 | C | C |
| 230 | D | C |
| 231 | C | C |
| 232 | C | C |
| 233 | C | C |
| 234 | C | C |
| 235 | C | C |
| 236 | C | C |
| 237 | D | C |
| 238 | C | C |
| 239 | C | C |
| 240 | D | C |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 241 | C | C |
| 242 | C | C |
| 243 | B | C |
| 244 | D | C |
| 245 | C | C |
| 246 | C | C |
| 247 | D | C |
| 248 | C | C |
| 249 | D | C |
| 250 | D | C |
| 251 | C | C |
| 252 | C | C |
| 253 | C | C |
| 254 | D | C |
| 255 | D | C |
| 256 | C | C |
| 257 | D | C |
| 258 | D | D |
| 259 | C | D |
| 260 | D | D |
| 261 | C | D |
| 262 | C | D |
| 263 | C | D |
| 264 | D | D |
| 265 | C | D |
| 266 | C | D |
| 267 | D | D |
| 268 | D | D |
| 269 | D | D |
| 270 | C | D |
| 271 | D | D |
| 272 | D | D |
| 273 | C | D |
| 274 | C | D |
| 275 | C | D |
| 276 | C | D |
| 277 | D | D |
| 278 | D | D |
| 279 | D | D |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 280 | D | D |
| 281 | D | D |
| 282 | D | D |
| 283 | D | D |
| 284 | D | D |
| 285 | D | D |
| 286 | D | D |
| 287 | D | D |
| 288 | D | D |
| 289 | D | D |
| 290 | D | D |
| 291 | D | D |
| 292 | D | D |
| 293 | D | D |
| 294 | D | D |
| 295 | D | D |
| 296 | D | D |
| 297 | D | D |
| 298 | D | D |
| 299 | D | D |
| 300 | D | D |
| 301 | D | D |
| 302 | D | D |
| 303 | D | D |
| 304 | D | D |
| 305 | D | D |
| 306 | D | D |
| 307 | D | D |
| 308 | D | D |
| 309 | D | D |
| 310 | D | D |
| 311 | D | D |
| 312 | D | D |
| 313 | D | D |
| 314 | D | D |
| 315 | D | D |
| 316 | D | D |
| 317 | C | D |
| 318 | C | D |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 319 | D | D |
| 320 | D | D |
| 321 | D | D |
| 322 | D | D |
| 323 | D | D |
| 324 | D | D |
| 325 | D | D |
| 326 | D | D |
| 327 | D | D |
| 328 | D | D |
| 329 | D | D |
| 330 | D | D |
| 331 | D | D |
| 332 | D | D |
| 333 | D | D |
| 334 | D | D |
| 335 | D | D |
| 336 | C | B |
| 337 | C | B |
| 338 | C | B |
| 339 | C | B |
| 340 | C | C |
| 341 | C | B |
| 342 | C | B |
| 343 | C | C |
| 344 | D | C |
| 345 | D | C |
| 346 | D | C |
| 347 | D | D |
| 348 | D | C |
| 349 | D | D |
| 350 | D | C |
| 351 | D | B |
| 352 | D | B |
| 353 | D | D |
| 354 | D | D |
| 355 | D | D |
| 356 | D | D |
| 357 | D | D |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 358 | D | D |
| 495 | B | A |
| 496 | B | A |
| 497 | B | A |
| 498 | B | B |
| 499 | B | A |
| 500 | B | A |
| 501 | B | A |
| 502 | B | A |
| 503 | B | A |
| 504 | B | A |
| 505 | B | A |
| 506 | B | A |
| 507 | B | A |
| 508 | B | A |
| 509 | B | A |
| 510 | B | A |
| 511 | B | A |
| 512 | B | B |
| 513 | B | A |
| 514 | B | A |
| 515 | B | A |
| 516 | B | A |
| 517 | B | A |
| 518 | B | A |
| 519 | B | A |
| 520 | B | A |
| 521 | B | A |
| 522 | B | A |
| 523 | B | B |
| 524 | C | A |
| 525 | B | B |
| 526 | C | A |
| 527 | B | B |
| 528 | B | B |
| 529 | B | B |
| 530 | B | A |
| 531 | B | A |
| 532 | B | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 533 | B | B |
| 534 | C | A |
| 535 | B | B |
| 536 | C | C |
| 537 | C | C |
| 538 | B | B |
| 539 | B | C |
| 540 | C | C |
| 541 | B | A |
| 542 | B | B |
| 543 | C | A |
| 544 | C | A |
| 545 | C | B |
| 546 | C | B |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 547 | C | B |
| 548 | C | C |
| 549 | C | C |
| 550 | C | B |
| 551 | C | B |
| 552 | C | C |
| 553 | C | C |
| 554 | C | C |
| 555 | C | C |
| 556 | C | C |
| 557 | B | A |
| 558 | B | A |
| 559 | C | A |
| 560 | B | A |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 561 | B | B |
| 562 | C | C |
| 563 | C | C |
| 564 | C | C |
| 565 | C | C |
| 566 | C | C |
| 567 | C | C |
| 568 | C | C |
| 569 | C | C |
| 570 | C | C |
| 571 | C | C |
| 572 | C | C |

Table 3

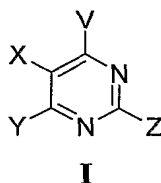
| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 573 | B | A |
| 574 | C | A |
| 575 | B | A |
| 576 | B | A |
| 577 | B | A |
| 578 | C | A |
| 579 | C | A |
| 580 | C | A |
| 581 | C | A |
| 582 | B | A |
| 583 | Bs | A |
| 584 | B | C |
| 585 | C | C |
| 586 | B | A |
| 587 | C | A |
| 588 | B | A |
| 589 | B | A |
| 590 | B | A |
| 591 | B | A |
| 592 | B | A |
| 593 | B | A |
| 594 | C | A |
| 595 | B | A |
| 596 | B | A |
| 597 | B | A |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 598 | B | A |
| 599 | B | A |
| 600 | B | B |
| 601 | B | A |
| 602 | B | A |
| 603 | B | A |
| 604 | B | A |
| 605 | B | A |
| 606 | B | A |
| 607 | B | A |
| 608 | B | A |
| 609 | B | A |
| 610 | B | A |
| 611 | B | A |
| 612 | B | A |
| 613 | B | A |
| 614 | B | A |
| 615 | B | A |
| 616 | B | A |
| 617 | B | A |
| 618 | B | A |
| 619 | B | B |
| 620 | B | B |
| 621 | B | A |
| 622 | B | A |

| Entry | IGF 0P | IGF 3P |
|-------|--------|--------|
| 623 | B | A |
| 624 | B | B |
| 625 | B | B |
| 626 | C | B |
| 627 | C | B |
| 628 | B | A |
| 629 | B | A |
| 630 | B | A |
| 631 | B | A |
| 632 | B | A |
| 633 | C | A |
| 634 | B | A |
| 635 | B | A |
| 636 | B | A |
| 637 | B | A |
| 638 | B | A |
| 639 | C | C |
| 640 | B | A |
| 641 | B | A |
| 642 | B | A |
| 643 | B | B |
| 644 | B | A |
| 645 | B | A |
| 646 | C | A |
| 647 | B | A |
| 648 | B | A |
| 649 | B | A |
| 650 | C | C |
| 651 | C | B |
| 652 | C | B |
| 653 | C | C |
| 654 | B | B |
| 655 | B | A |
| 656 | B | A |
| 657 | B | A |
| 658 | B | A |
| 659 | B | A |
| 660 | B | B |
| 661 | B | A |
| 662 | B | A |
| 663 | B | A |

We claim:

1. A compound of Formula I,



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

V is NR_1R_{1a} , or O-R_1 , wherein

R_1 is H, CN, halo, $-\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{NR}_{13}\text{R}_{14}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6$ alkyl- R_{20} , wherein R_{20} is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, $\text{C}_3\text{-C}_7$ heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from $\text{C}_1\text{-C}_6$ alkyl, and $-\text{C}_0\text{-C}_6$ alkyl- R_{21} ;

R_{1a} is H or $\text{C}_1\text{-C}_6$ alkyl; or

when V is NR_1R_{1a} , R_1 and R_{1a} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing, in addition to the nitrogen, up to two additional heteroatoms independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}_{13}\text{R}_{14}$ or $\text{C}_3\text{-C}_7$ cycloalkyl;

X is H, halo, $\text{C}_1\text{-C}_6$ alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, or $\text{N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl;

Y is H, halo, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_6$ alkyl- $\text{NR}_{15}\text{R}_{16}$, $\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, $-\text{O-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6\text{-alkyl-R}_{21}$, $-\text{O-R}_{21}$, $-\text{C}(\text{O})\text{-R}_{21}$, $-\text{O-(CH}_2)_n\text{-R}_{21}$, $-\text{C}(\text{O})\text{-NR}_{13}\text{R}_{14}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-aryl}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-aryl}$, $-\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-heterocyclyl}$;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, $\text{C}_1\text{-C}_6$ alkyl, aryl-

C₁-C₆ alkyl-, aryl-(CH₂)_n-O-(CH₂)_n-aryl-, arylOH, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, or a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is NR₁₃R₁₄, N(R₁₃)C(O)-C₁-C₆ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, C(O)O-(CH₂)_n-phenyl, and C(O)-C₁-C₆ alkyl;

Z is H, NR₂R₃, -S-R_{2a}, or -O-R_{2a}, wherein

R₂ is -C₁-C₆ alkyl, -C₁-C₆ alkyl-NR₁₃R₁₄, -C(O)-aryl, -C₀-C₆-alkyl-aryl, -C₀-C₆-alkyl-heteroaryl, -C₀-C₆-alkyl-(C₃-C₇-cycloalkyl), -C₀-C₆-alkyl-heterocyclyl, or -C₀-C₆ alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein

each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, C₃-C₇ cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO₂, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, N(R₁₃)C(O)-C₁-C₆ alkyl, -SO₂NR₁₃R₁₄, -O-C(O)-NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, -O-(CH₂)_n-NR₁₅R₁₆, -C₁-C₆ alkyl-NR₁₃R₁₄, -N(R₁₃)-C(O)-C₁-C₆ alkyl, -N(R₁₃)-C(O)-aryl, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-aryl, -O-(CH₂)_n-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-C(O)-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-O-C₁-C₆ alkyl, -C₀-C₆ alkyl-N(R₁₃)-C(O)O-C₁-C₆ alkyl, -C₀-C₆alkyl-C(O)-heterocyclyl, -C₀-C₆alkyl-C(O)-heteroaryl, -C₀-C₆alkyl-C(O)-aryl, -C₀-C₆-alkyl-R₂₁, aryloxy, -O-(CH₂)_n-R₂₁, -SO₂-heterocyclyl, N(R₁₃)-C(O)-C₃-C₇-cycloalkyl, -C₀-C₆alkyl C(O)O-R₂₁, C₃-

C₇-cycloalkyl, -C₀-C₆alkylR₂₁, -SC₁-C₆alkyl or C₁-C₆ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, CF₃, C₁-C₆ alkyl, C₁-C₆ haloalkoxy, NR₁₃R₁₄ and C₁-C₆ alkoxy;

R₃ is H or C₁-C₆ alkyl;

or R₂ and R₃ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing up to three heteroatoms independently selected from O, N, and S, and wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two of halo or C₁-C₆ alkyl;

R_{2a} is aryl or C₀-C₆ alkyl-heteroaryl, wherein the aryl and heteroaryl are optionally substituted with aryl, -N(R₁₃)-C(O)-C₃-C₇ cycloalkyl or -C(O)NR₁₃R₁₄;

R₁₃ and R₁₄ are independently H or C₁-C₆ alkyl;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, or -C(O)O-C₁-C₆ alkyl;

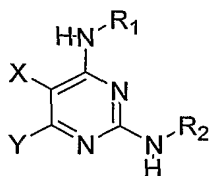
R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

n is 0-6;

provided that when V is NH₂, X, Y and Z are not simultaneously H.

2. The compound according to claim 1 wherein V is NHR₁.
3. The compound according to claim 1 wherein Z is NR₂R₃.
4. The compound according to claim 1 wherein V is NHR₁ and Z is NR₂R₃.

5. A compound of Formula II,



II

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R₁ is H, CN, halo, -NR₁₃R₁₄, C(O)NR₁₃R₁₄, C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C₀-C₆ alkyl-R₂₀, wherein R₂₀ is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, C₃-C₇ heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, and -C₀-C₆ alkyl-R₂₁;

X is H, halo, C₁-C₆ alkyl, NO₂, mono-, di-, or tri-halo substituted methyl, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, or N(R₁₃)-C(O)-C₁-C₆ alkyl;

Y is H, halo, OH, C₁-C₆ alkyl, NR₁₅R₁₆, C₁-C₆ alkoxy, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -C(O)-C₁-C₆ alkyl, -C₀-C₆-alkyl-R₂₁, -O-R₂₁, -C(O)-R₂₁, -O-(CH₂)_n-R₂₁, -C(O)-NR₁₃R₁₄, -C(O)-N(R₁₃)-aryl, -C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)-N(R₁₃)-(CH₂)_n-aryl, -C(O)-N(R₁₃)-(CH₂)_n-heterocyclyl, wherein R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, aryl-C₁-C₆ alkyl-, aryl-(CH₂)_n-O-(CH₂)_n-aryl-, arylOH, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is $\text{NR}_{13}\text{R}_{14}$, $\text{N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties independently selected from halo, $\text{C}(\text{O})\text{O}(\text{CH}_2)_n\text{-phenyl}$, and $\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl;

R_2 is $\text{-C}_1\text{-C}_6$ alkyl, $\text{-C}_1\text{-C}_6$ alkyl- $\text{NR}_{13}\text{R}_{14}$, $\text{-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-heteroaryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-(C}_3\text{-C}_7\text{-cycloalkyl)}$, $\text{-C}_0\text{-C}_6\text{-alkyl-heterocyclyl}$, or $\text{-C}_0\text{-C}_6$ alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, $\text{C}_3\text{-C}_7$ cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO_2 , $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, $\text{N}(\text{R}_{13})\text{C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $\text{-SO}_2\text{NR}_{13}\text{R}_{14}$, $\text{-O-C}(\text{O})\text{-NR}_{13}\text{R}_{14}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ thioalkoxy, $\text{-O-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_1\text{-C}_6$ alkyl- $\text{NR}_{13}\text{R}_{14}$, $\text{-N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_1\text{-C}_6$ alkyl, $\text{-N}(\text{R}_{13})\text{-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-aryl}$, $\text{-O-(CH}_2)_n\text{-C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $\text{-O-(CH}_2)_n\text{-C}(\text{O})\text{-NR}_{15}\text{R}_{16}$, $\text{-C}_0\text{-C}_6$ alkyl- $\text{C}(\text{O})\text{-N}(\text{R}_{13})\text{-(CH}_2)_n\text{-O-C}_1\text{-C}_6$ alkyl, $\text{-C}_0\text{-C}_6$ alkyl- $\text{N}(\text{R}_{13})\text{-C}(\text{O})\text{O-C}_1\text{-C}_6$ alkyl, $\text{-C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heterocyclyl}$, $\text{-C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-heteroaryl}$, $\text{-C}_0\text{-C}_6\text{alkyl-C}(\text{O})\text{-aryl}$, $\text{-C}_0\text{-C}_6\text{-alkyl-R}_{21}$, aryloxy, $\text{-O-(CH}_2)_n\text{-R}_{21}$, $\text{-SO}_2\text{-heterocyclyl}$, $\text{N}(\text{R}_{13})\text{-C}(\text{O})\text{-C}_3\text{-C}_7\text{-cycloalkyl}$, $\text{-C}_0\text{-C}_6\text{alkyl C}(\text{O})\text{O-R}_{21}$, $\text{C}_3\text{-C}_7\text{-cycloalkyl}$, $\text{-C}_0\text{-C}_6\text{alkylR}_{21}$, $\text{-SC}_1\text{-C}_6\text{alkyl}$ or $\text{C}_1\text{-C}_6$ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{NR}_{13}\text{NR}_{14}$ and $\text{C}_1\text{-C}_6$ alkoxy;

R_{13} and R_{14} are independently H or $\text{C}_1\text{-C}_6$ alkyl, or R_{13} and R_{14} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently

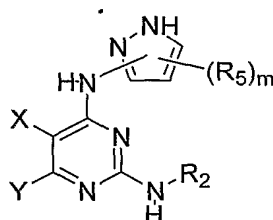
selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or -C(O)O-C₁-C₆ alkyl; and

n is 1-6.

6. The compound according to claim 5 wherein X is H, C₁-C₆ alkyl, or halo.
7. The compound according to claim 5 wherein X is H or halo.
8. The compound according to claim 5 wherein X is halo.
9. The compound according to claim 5 wherein Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-R₂₁, -O-(CH₂)_n-R₂₁, or aryl.
10. The compound according to claim 5 wherein Y is H.
11. The compound according to claim 5 wherein Y is halo.
12. The compound according to claim 5 wherein Y is C₁-C₆ alkyl.
13. The compound according to claim 5 wherein R₁ is aryl or heteroaryl optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, and heteroaryl.
14. The compound according to claim 5 wherein R₁ is heteroaryl, optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl, and heteroaryl.

15. The compound according to claim 5 wherein R_1 is pyrazolyl or isoxazolyl, optionally substituted with one, two, or three groups independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, and heteroaryl.
16. The compound according to claim 5 wherein R_2 is aryl or $-C_1$ - C_6 -alkyl-heteroaryl.
17. The compound according to claim 5 wherein R_2 is C_1 - C_6 -alkyl-heteroaryl, optionally substituted.
18. The compound according to claim 17 wherein R_2 is C_1 - C_2 -isoxazolyl, optionally substituted with aryl, heterocyclyl, or C_1 - C_6 alkyl.
19. The compound according to claim 5 wherein R_2 is aryl, optionally substituted.
20. The compound according to claim 19 wherein R_2 is phenyl, optionally substituted with - O -(CH_2) $_n$ - $NR_{15}R_{16}$, $NR_{13}R_{14}$, $-C_0$ - C_6 alkyl- $C(O)NR_{15}R_{16}$, $-C_0$ - C_6 alkyl- $C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $N(R_{13})C(O)-C_1$ - C_6 alkyl, halo, $-C_1$ - C_6 alkyl- $NR_{13}R_{14}$, C_1 - C_6 alkoxy, or heterocyclyl.
21. A compound of Formula III,



III

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

m is 1 or 2;

R_5 at each occurrence is independently H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl;

X is H, halo, C_1 - C_6 alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $NR_{13}R_{14}$, $C(O)O-C_1$ - C_6 alkyl, or $N(R_{13})-C(O)-C_1$ - C_6 alkyl;

Y is H, halo, OH, C_1 - C_6 alkyl, $NR_{15}R_{16}$, C_1 - C_6 alkoxy, $-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C(O)O-C_1$ - C_6 alkyl, $-O-(CH_2)_n-NR_{15}R_{16}$, $-C(O)-C_1$ - C_6 alkyl, $-C_0$ - C_6 -alkyl- R_{21} , $-O-R_{21}$, $-C(O)-R_{21}$, $-O-(CH_2)_n-R_{21}$, $-C(O)-NR_{13}R_{14}$, $-C(O)-N(R_{13})$ -aryl, $-C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C(O)-$

$N(R_{13})-(CH_2)_n$ -aryl, $-C(O)-N(R_{13})-(CH_2)_n$ -heterocyclyl, wherein R_{21} is heterocyclyl, aryl, heteroaryl, or C_3 - C_7 cycloalkyl, and wherein alkyl, aryl, heteroaryl, C_3 - C_7 cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C_1 - C_6 alkyl, $NR_{13}R_{14}$, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyl-, aryl- $(CH_2)_n$ -O-aryl-, C_3 - C_7 cycloalkyl, heterocyclyl, -aryl- $N(R_{13})C(O)-C_3$ - C_7 cycloalkyl- $C(O)-N(R_{14})$ -aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C_3 - C_7 cycloalkyl,

M is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl,

Q is $NR_{13}R_{14}$, $N(R_{13})C(O)-C_1$ - C_6 alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and

Y is optionally further substituted with one or two moieties independently selected from halo, $C(O)O-(CH_2)_n$ -phenyl, and $C(O)-C_1$ - C_6 alkyl;

R_2 is $-C_1$ - C_6 alkyl, $-C_1$ - C_6 alkyl- $NR_{13}R_{14}$, $-C(O)$ -aryl, $-C_0$ - C_6 -alkyl-aryl, $-C_0$ - C_6 -alkyl-heteroaryl, $-C_0$ - C_6 -alkyl- $(C_3$ - C_7 -cycloalkyl), $-C_0$ - C_6 -alkyl-heterocyclyl, or $-C_0$ - C_6 alkyl-5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein each alkyl is optionally substituted with phenyl, and

each aryl, heteroaryl, C_3 - C_7 cycloalkyl, heterocyclyl, or 5-12 membered ring system is optionally substituted with one, two, or three groups independently selected from halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO_2 , $NR_{13}R_{14}$, $C(O)O-C_1$ - C_6 alkyl, $N(R_{13})C(O)-C_1$ - C_6 alkyl, $-SO_2NR_{13}R_{14}$, $-O-C(O)-NR_{13}R_{14}$, $-C_0$ - C_6 alkyl- $C(O)NR_{15}R_{16}$, C_1 - C_6 alkoxy, C_1 - C_6 thioalkoxy, $-O-(CH_2)_n-NR_{15}R_{16}$, $-C_1$ - C_6 alkyl- $NR_{13}R_{14}$, $-N(R_{13})-C(O)-C_1$ - C_6 alkyl, $-N(R_{13})-C(O)$ -aryl, $-C_0$ - C_6 alkyl- $C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-C_0$ - C_6 alkyl- $C(O)-N(R_{13})-(CH_2)_n$ -aryl, $-O-(CH_2)_n-C(O)-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-O-(CH_2)_n-C(O)-NR_{15}R_{16}$, $-C_0$ - C_6 alkyl- $C(O)-$

$N(R_{13})-(CH_2)_n-O-C_1-C_6$ alkyl, $-C_0-C_6$ alkyl- $N(R_{13})-C(O)O-C_1-C_6$ alkyl, $-C_0-C_6$ alkyl- $C(O)$ -heterocyclyl, $-C_0-C_6$ alkyl- $C(O)$ -heteroaryl, $-C_0-C_6$ alkyl- $C(O)$ -aryl, $-C_0-C_6$ -alkyl- R_{21} , aryloxy, $-O-(CH_2)_n-R_{21}$, $-SO_2$ -heterocyclyl, $N(R_{13})-C(O)-C_3-C_7$ -cycloalkyl, or C_1-C_6 alkyl optionally substituted with halo or cyano,,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

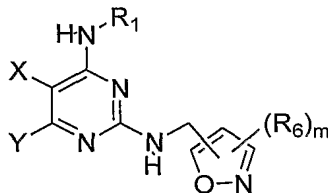
R_{13} and R_{14} are independently H or C_1-C_6 alkyl, or R_{13} and R_{14} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R_{15} and R_{16} are independently H, C_1-C_6 alkyl, heteroaryl, or heterocyclyl, or R_{15} and R_{16} together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties independently selected from halo, C_1-C_6 alkyl, and $-C(O)O-C_1-C_6$ alkyl; and

n is 1-6.

22. The compound according to claim 21 wherein X is H, C_1-C_6 alkyl, or halo.
23. The compound according to claim 21 wherein X is H or halo.
24. The compound according to claim 21 wherein X is halo.
25. The compound according to claim 21 wherein Y is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, $NR_{15}R_{16}$, $-C(O)O-C_1-C_6$ alkyl, $-O-(CH_2)_n-NR_{15}R_{16}$, $-N(R_{13})-(CH_2)_n-NR_{15}R_{16}$, $-O-(CH_2)_n-R_{21}$, $-O-R_{21}$, or aryl.
26. The compound according to claim 21 wherein Y is H.
27. The compound according to claim 21 wherein Y is halo.

28. The compound according to claim 21 wherein Y is C₁-C₆ alkyl.
29. The compound according to claim 21 wherein R₂ is aryl or -C₁-C₆-alkyl-heteroaryl, wherein aryl or heteroaryl are optionally substituted.
30. The compound according to claim 21 wherein R₂ is C₁-C₆-alkyl-heteroaryl, optionally substituted.
31. The compound according to claim 30 wherein R₂ is C₁-C₂-isoxazolyl, optionally substituted with 1 or 2 of aryl, heterocyclyl, or C₁-C₆ alkyl.
32. The compound according to claim 21 wherein R₂ is aryl, optionally substituted.
33. The compound according to claim 32 wherein R₂ is phenyl, optionally substituted with 1 or 2 of -O-(CH₂)_n-NR₁₅R₁₆, NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, N(R₁₃)C(O)-C₁-C₆ alkyl, halo, -C₁-C₆ alkyl-NR₁₃R₁₄, C₁-C₆ alkoxy, or heterocyclyl.
34. A compound of Formula IV,



IV

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

- R₁ is H, CN, halo, -NR₁₃R₁₄, C(O)NR₁₃R₁₄, C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C₀-C₆ alkyl-R₂₀, wherein R₂₀ is aryl, heteroaryl, heterocyclyl, or a 5-12 membered fused bicyclic or tricyclic saturated, partially saturated, or unsaturated ring system containing 0-4 ring atoms selected from N, O, and S, wherein aryl, heteroaryl, C₃-C₇ heterocyclyl, or the 5-12 membered ring system are optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, and -C₀-C₆ alkyl-R₂₁;
- X is H, halo, C₁-C₆ alkyl, NO₂, mono-, di-, or tri-halo substituted methyl, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, or N(R₁₃)-C(O)-C₁-C₆ alkyl;

Y is H, halo, OH, C₁-C₆ alkyl, NR₁₅R₁₆, C₁-C₆ alkoxy, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -C(O)-C₁-C₆ alkyl, -C₀-C₆-alkyl-R₂₁, -O-R₂₁, -C(O)-R₂₁, -O-(CH₂)_n-R₂₁, -C(O)-NR₁₃R₁₄, -C(O)-N(R₁₃)-aryl, -C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)-N(R₁₃)-(CH₂)_n-aryl, -C(O)-N(R₁₃)-(CH₂)_n-heterocyclyl, wherein R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, aryl-C₁-C₆ alkyl-, aryl-(CH₂)_n-O-aryl-, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is NR₁₃R₁₄, N(R₁₃)C(O)-C₁-C₆ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, and heterocyclyl substituent on the group formed by X and

Y is optionally further substituted with one or two moieties selected from halo, C(O)O-(CH₂)_n-phenyl, and C(O)-C₁-C₆ alkyl;

R₆ at each occurrence is independently H, halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO₂, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, N(R₁₃)C(O)-C₁-C₆ alkyl, -SO₂NR₁₃R₁₄, -O-C(O)-NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, -O-(CH₂)_n-NR₁₅R₁₆, -C₁-C₆ alkyl-NR₁₃R₁₄, -N(R₁₃)-C(O)-C₁-C₆ alkyl, -N(R₁₃)-C(O)-aryl, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-aryl, -O-(CH₂)_n-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-C(O)-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-O-C₁-C₆ alkyl, -C₀-C₆ alkyl-N(R₁₃)-C(O)O-C₁-C₆ alkyl, -C₀-C₆alkyl-C(O)-heterocyclyl, -C₀-C₆alkyl-C(O)-heteroaryl, -C₀-C₆alkyl-C(O)-aryl, -C₀-C₆-alkyl-R₂₁, aryloxy, -O-(CH₂)_n-R₂₁, -SO₂-heterocyclyl, N(R₁₃)-C(O)-C₃-C₇-cycloalkyl, or C₁-C₆ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl substituent is further optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

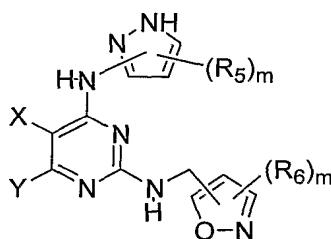
R₁₃ and R₁₄ are independently H or C₁-C₆ alkyl, or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, or -C(O)O-C₁-C₆ alkyl; and

m is 1 or 2; and n is 1-6.

35. The compound according to claim 34 wherein X is H, C₁-C₆ alkyl, or halo.
36. The compound according to claim 34 wherein X is H or halo.
37. The compound according to claim 34 wherein X is halo.
38. The compound according to claim 34 wherein Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-R₂₁, -O-R₂₁, or aryl.
39. The compound according to claim 34 wherein Y is H.
40. The compound according to claim 34 wherein Y is halo.
41. The compound according to claim 34 wherein Y is C₁-C₆ alkyl.

42. The compound according to claim 34 wherein R_1 is aryl or heteroaryl optionally substituted with one, two, or three groups independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl.
43. The compound according to claim 34 wherein R_1 is heteroaryl, optionally substituted with one, two, or three groups independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl.
44. The compound according to claim 34 wherein R_1 is pyrazolyl or isoxazolyl, optionally substituted with one, two, or three groups independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl.
45. The compound according to claim 34 wherein m is 1 and R_6 is aryl, heterocyclyl, or C_1 - C_6 alkyl.
46. A compound of Formula V,



V

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, m is independently 1 or 2;

R_5 at each occurrence is independently H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl; X is H, halo, C_1 - C_6 alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $NR_{13}R_{14}$, $C(O)O$ - C_1 - C_6 alkyl, or $N(R_{13})$ - $C(O)$ - C_1 - C_6 alkyl;

Y is H, halo, OH, C_1 - C_6 alkyl, $NR_{15}R_{16}$, C_1 - C_6 alkoxy, $-N(R_{13})$ -(CH_2) $_n$ - $NR_{15}R_{16}$, $-C(O)O$ - C_1 - C_6 alkyl, $-O$ -(CH_2) $_n$ - $NR_{15}R_{16}$, $-C(O)$ - C_1 - C_6 alkyl, $-C_0$ - C_6 -alkyl- R_{21} , $-O$ - R_{21} , $-C(O)$ - R_{21} , $-O$ -(CH_2) $_n$ - R_{21} , $-C(O)$ - $NR_{13}R_{14}$, $-C(O)$ - $N(R_{13})$ -aryl, $-C(O)$ - $N(R_{13})$ -(CH_2) $_n$ - $NR_{15}R_{16}$, $-C(O)$ - $N(R_{13})$ -(CH_2) $_n$ -aryl, $-C(O)$ - $N(R_{13})$ -(CH_2) $_n$ -heterocyclyl, wherein R_{21} is heterocyclyl, aryl, heteroaryl, or C_3 - C_7 cycloalkyl, and wherein alkyl, aryl, heteroaryl, C_3 - C_7 cycloalkyl, and

heterocyclyl are optionally substituted with one or two moieties independently selected from halo, C₁-C₆ alkyl, NR₁₃R₁₄, and heterocyclyl;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S, wherein the heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, aryl-C₁-C₆ alkyl-, aryl-(CH₂)_n-O-aryl-, C₃-C₇ cycloalkyl, heterocyclyl, -aryl-N(R₁₃)C(O)-C₃-C₇ cycloalkyl-C(O)-N(R₁₄)-aryl, and a group of the formula -L-M-Q, wherein

L is a bond or C₃-C₇ cycloalkyl,

M is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl,

Q is NR₁₃R₁₄, N(R₁₃)C(O)-C₁-C₆ alkyl, heterocyclyl, or a saturated fused bicyclic ring containing one or two heteroatoms independently selected from O, N, and S,

wherein each aryl, heteroaryl, or heterocyclyl substituent on the group formed by X and Y is optionally further substituted with one or two moieties selected from halo, C(O)O-(CH₂)_n-phenyl, and C(O)-C₁-C₆ alkyl;

R₆ at each occurrence is independently H, halo, mono-, di-, or tri-halo substituted methyl or methoxy, CN, NO₂, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, N(R₁₃)C(O)-C₁-C₆ alkyl, -SO₂NR₁₃R₁₄, -O-C(O)-NR₁₃R₁₄, -C₀-C₆ alkyl-C(O)NR₁₅R₁₆, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, -O-(CH₂)_n-NR₁₅R₁₆, -C₁-C₆ alkyl-NR₁₃R₁₄, -N(R₁₃)-C(O)-C₁-C₆ alkyl, -N(R₁₃)-C(O)-aryl, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-aryl, -O-(CH₂)_n-C(O)-N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-C(O)-NR₁₅R₁₆, -C₀-C₆ alkyl-C(O)-N(R₁₃)-(CH₂)_n-O-C₁-C₆ alkyl, -C₀-C₆ alkyl-N(R₁₃)-C(O)O-C₁-C₆ alkyl, -C₀-C₆alkyl-C(O)-heterocyclyl, -C₀-C₆alkyl-C(O)-heteroaryl, -C₀-C₆alkyl-C(O)-aryl, -C₀-C₆-alkyl-R₂₁, aryloxy, -O-(CH₂)_n-R₂₁, -SO₂-heterocyclyl, N(R₁₃)-C(O)-C₃-C₇-cycloalkyl, or C₁-C₆ alkyl optionally substituted with halo or cyano,

wherein each aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with 1-3 groups independently selected from halo, mono-, di-, or tri-halo substituted methyl, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

R₁₃ and R₁₄ are independently H or C₁-C₆ alkyl, or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl or heteroaryl group is optionally substituted with one or two of halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl, heteroaryl, or heterocyclyl, or R₁₅ and R₁₆ together with the nitrogen to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group wherein one or two ring carbons are each optionally replaced with a heteroatom independently selected from O, N, and S, and wherein each heterocyclyl and heteroaryl group is optionally substituted with one or two moieties selected from halo, C₁-C₆ alkyl, and -C(O)O-C₁-C₆ alkyl; and

n is 1-6.

47. The compound according to claim 46 wherein X is H, C₁-C₆ alkyl, or halo.

48. The compound according to claim 46 wherein X is H or halo.

49. The compound according to claim 46 wherein X is halo.

50. The compound according to claim 46 wherein Y is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-R₂₁, -O-R₂₁, or aryl.

51. The compound according to claim 46 wherein Y is H.

52. The compound according to claim 46 wherein Y is halo.

53. The compound according to claim 46 wherein Y is C₁-C₆ alkyl.

54. The compound according to claim 46 wherein m is 1 and R₆ is aryl, heterocyclyl, or C₁-C₆ alkyl.

55. A compound according to claim 1, wherein,
V is NR₁R_{1a}, wherein

R₁ is -C₀-C₆ alkyl-R₂₀, wherein R₂₀ heteroaryl, wherein the heteroaryl is optionally substituted with one, two, or three groups independently selected from C₁-C₆ alkyl, and -C₀-C₆ alkyl-R₂₁;

R_{1a} is H;

X is H, or halo;

Y is H, C₁-C₆ alkyl, NR₁₅R₁₆, C₀-C₆ alkyl-NR₁₅R₁₆, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -O-(CH₂)_n-NR₁₅R₁₆, -C₀-C₆-alkyl-R₂₁, -O-R₂₁ or -O-(CH₂)_n-R₂₁;

Z is NR₂R₃, or -O-R_{2a}, wherein

R₂ is -C₀-C₆-alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with one, two, or three groups independently selected from -C₀-C₆-alkyl-R₂₁ or C₁-C₆ alkyl;

R₃ is H;

R_{2a} is C₀-C₆ alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with aryl;

R₁₃ is H;

R₁₅ and R₁₆ are independently H, C₁-C₆ alkyl or heterocyclyl optionally substituted with C₁-C₆ alkyl;

R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl or NR₁₃R₁₄; and

n is 1-4.

56. The compound according to claim 55, wherein Z is NR₂R₃.

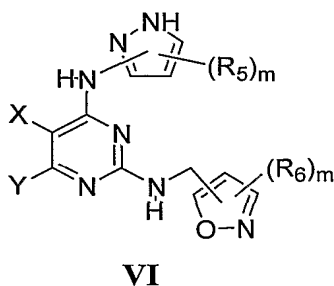
57. The compound according to claim 56, wherein R₂ is -C₁-C₃-alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with R₂₁ or C₁-C₄ alkyl.

58. The compound according to claim 57, wherein the C₁-C₄ alkyl is methyl, propyl or isopropyl.

59. The compound according to claim 57, wherein the R₂₁ is heteroaryl or aryl wherein the heteroaryl and aryl are optionally substituted with halo or NH₂.

60. The compound according to claim 59, wherein the halo is fluoro.

61. The compound according to claim 55, wherein Z is -O-R_{2a}.
62. The compound according to claim 55, wherein R_{2a} is C₁-C₂ alkyl-heteroaryl, wherein the heteroaryl is optionally substituted with phenyl.
63. The compound according to claim 55, wherein R₁ is heteroaryl optionally substituted with C₁-C₄ alkyl or R₂₁.
64. The compound according to claim 63, wherein the C₁-C₄ alkyl is methyl, propyl, isopropyl.
65. The compound according to claim 63, wherein the R₂₁ is C₃-C₄ cycloalkyl.
66. The compound according to claim 63, wherein the R₂₁ is cyclopropyl.
67. The compound according to claim 55, wherein the X is chloro.
68. The compound according to claim 55, wherein Y is C₁-C₄ alkyl, NR₁₅R₁₆, C₁-C₄ alkyl-NR₁₅R₁₆, -N(H)-(CH₂)₂₋₃-NR₁₅R₁₆, -O-(CH₂)₂-NR₁₅R₁₆, -R₂₁, -O-R₂₁ or -O-(CH₂)₂-R₂₁.
69. The compound according to claim 68, wherein R₁₅ and R₁₆ are independently H, C₁-C₄ alkyl or heterocyclyl optionally substituted with C₁-C₃ alkyl.
70. The compound according to claim 69, wherein R₁₅ and R₁₆ are independently methyl, ethyl, propyl, heterocyclyl optionally substituted with methyl, ethyl or propyl.
71. The compound according to claim 68, wherein R₂₁ is heterocyclyl optionally substituted with one or two moieties independently selected from -S(O)₂-C₁-C₃ alkyl, -C(O)-C₁-C₃ alkyl, -C(O)-H, C₁-C₂ alkyl-aryl, or C₁-C₄ alkyl.
72. The compound according to claim 71, wherein R₂₁ is optionally substituted with one or two moieties independently selected from -S(O)₂-CH₃, -C(O)-CH₃, -CH₂-phenyl, methyl, ethyl or propyl.
73. A compound of Formula VI,



wherein,

m is 1 or 2 or 3;

R₅ is C₁-C₆ alkyl, and -C₀-C₆ alkyl-R₂₁;

X is H, or halo;

Y is -C₀-C₆-alkyl-R₂₁;

R₆ is -C₀-C₆-alkyl-R₂₁ or C₁-C₆ alkyl;

R₂₁ is heterocyclyl, aryl, heteroaryl, or C₃-C₇ cycloalkyl, and wherein alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, and heterocyclyl are optionally substituted with one or two moieties independently selected from halo, -S(O)₂-C₀-C₁ alkyl, -C(O)-C₀-C₁ alkyl, -C(O)-H, -C₀-C₁ alkyl-aryl, C₁-C₆ alkyl or NR₁₃R₁₄.

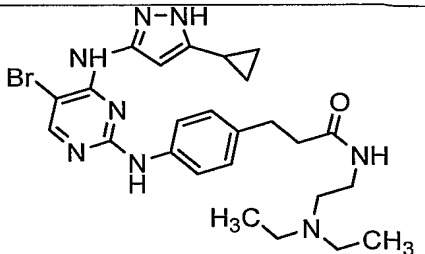
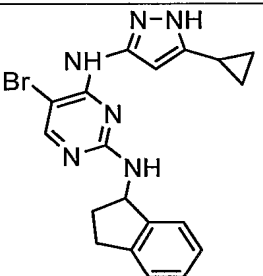
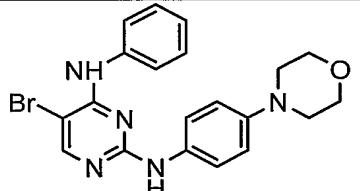
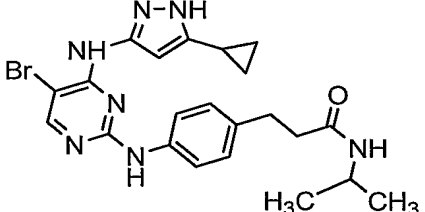
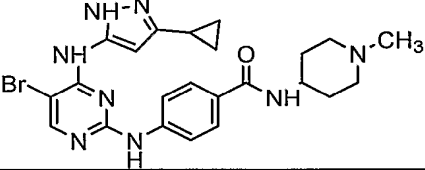
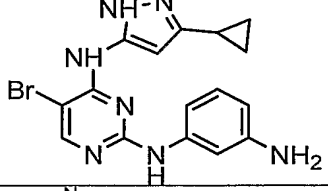
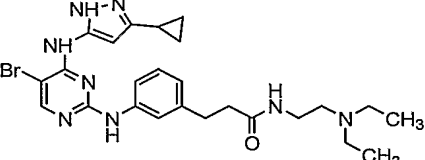
74. The compound according to claim 73, wherein Y is heterocyclyl optionally substituted with C₁-C₃ alkyl, X is H or halo, R₅ is C₃-C₄ cycloalkyl and R₆ is C₁-C₄ alkyl.
75. The compound according to claim 74, wherein Y is heterocyclyl optionally substituted with methyl, ethyl, propyl or isopropyl, X is H, R₅ is cyclopropyl and R₆ is methyl, ethyl, propyl or isopropyl.
76. A compound, or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, selected from the following:

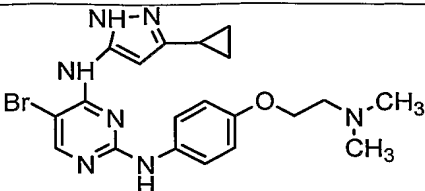
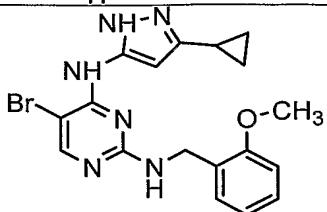
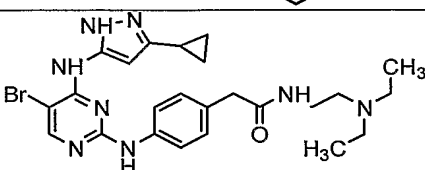
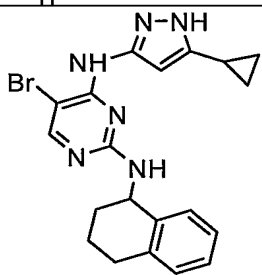
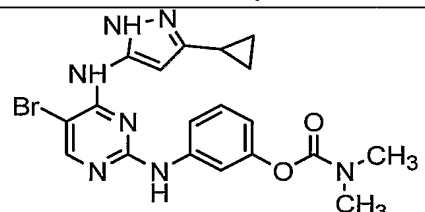
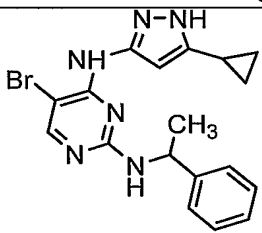
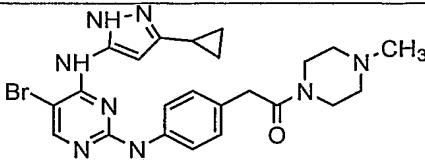
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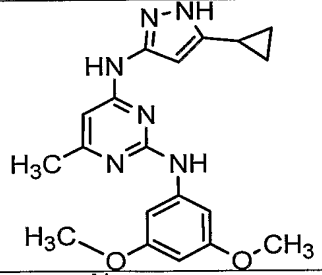
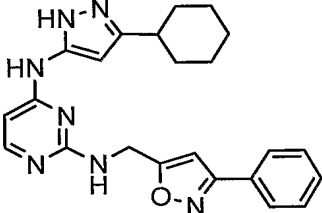
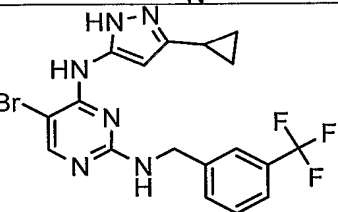
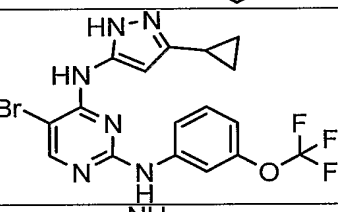
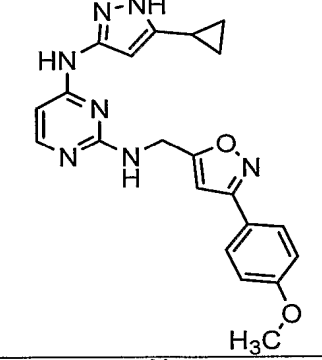
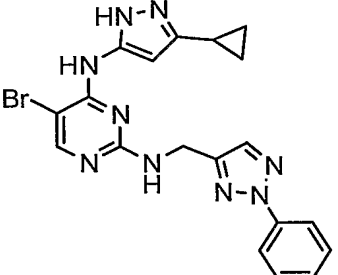
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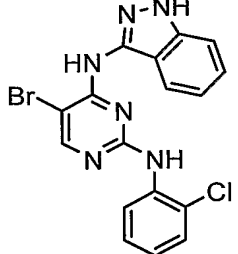
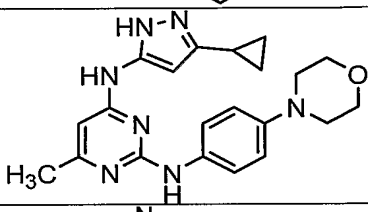
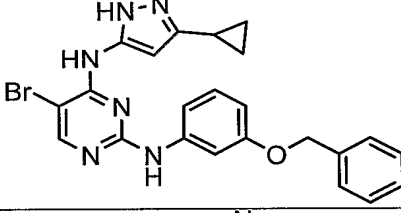
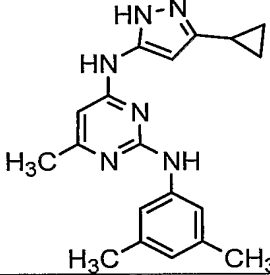
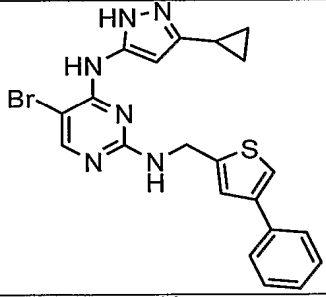
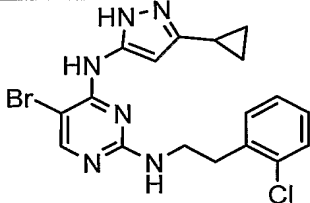
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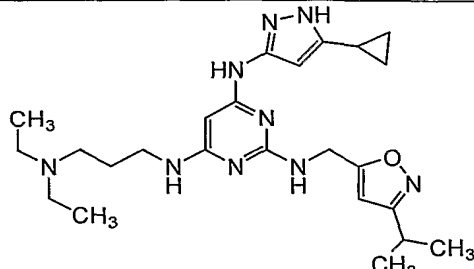
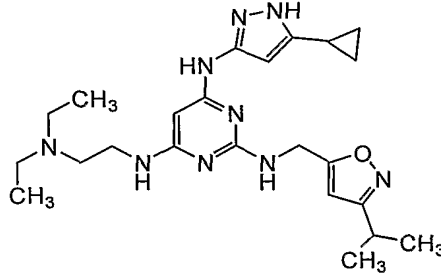
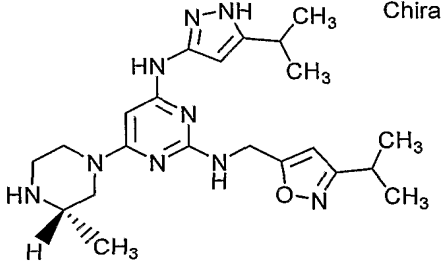
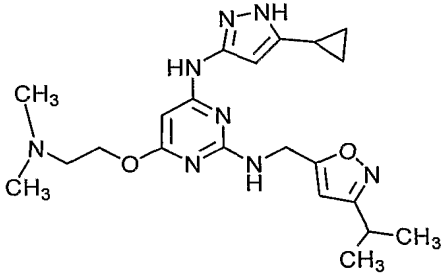
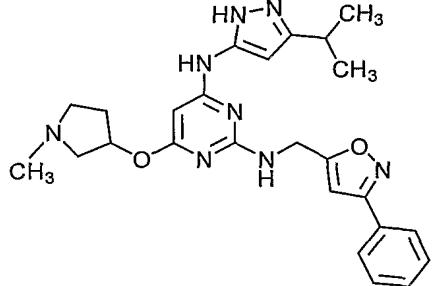
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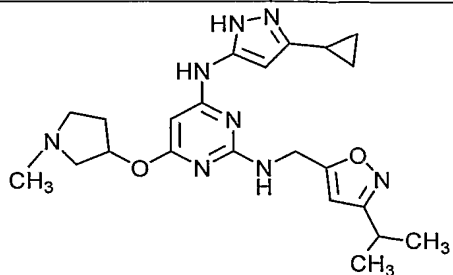
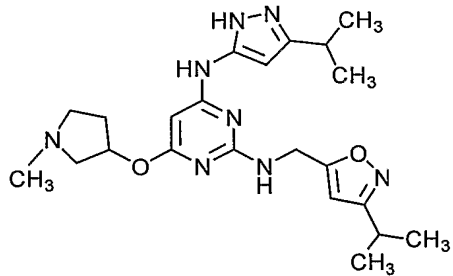
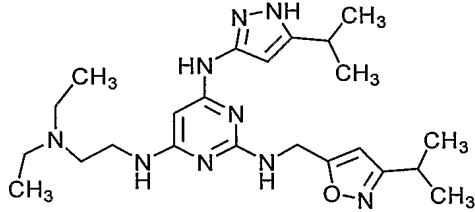
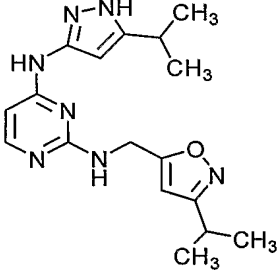
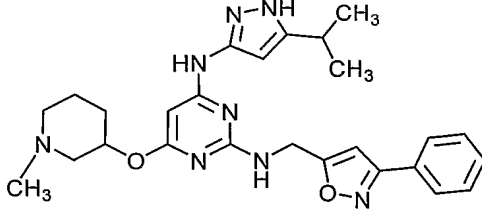
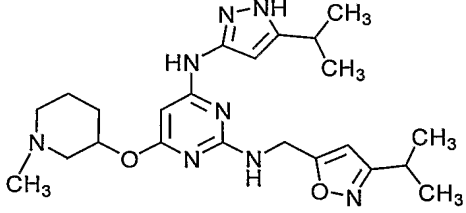
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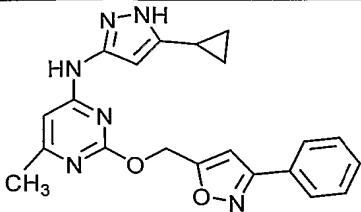
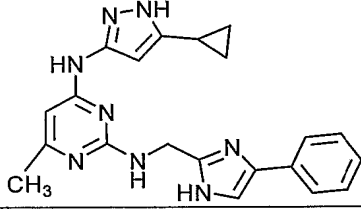
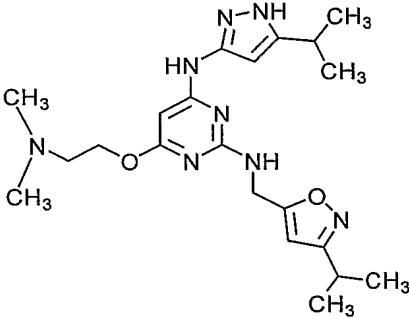
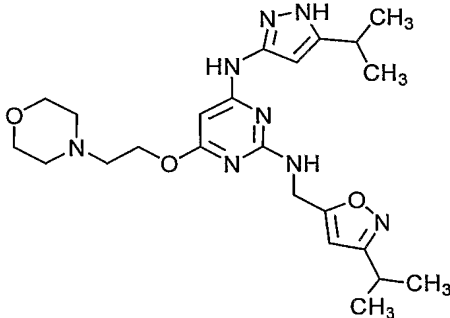
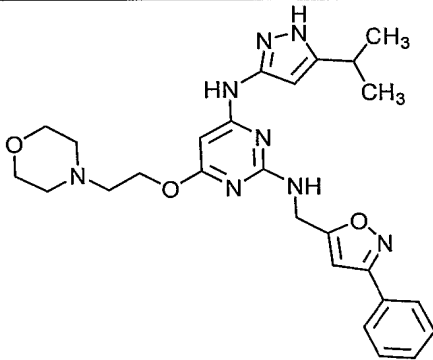
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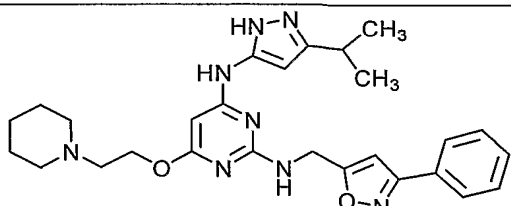
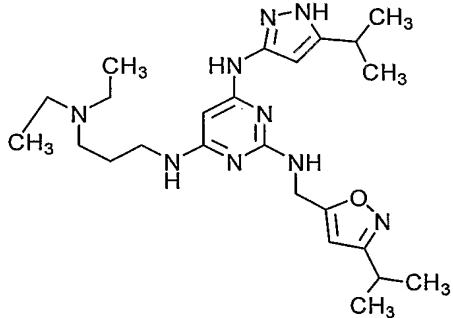
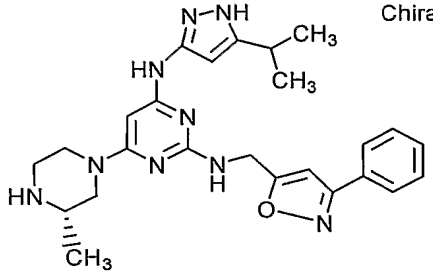
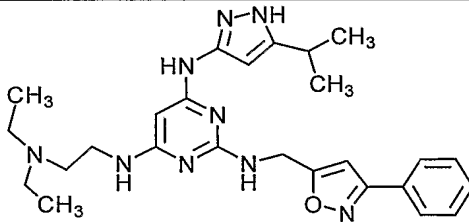
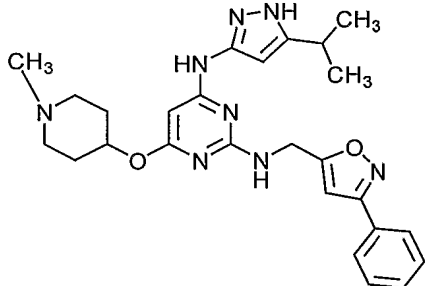
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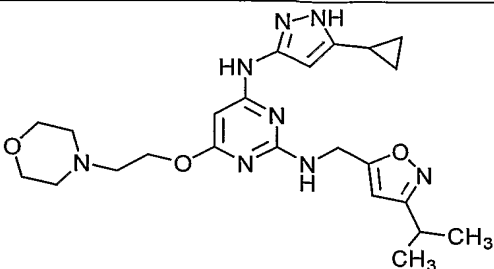
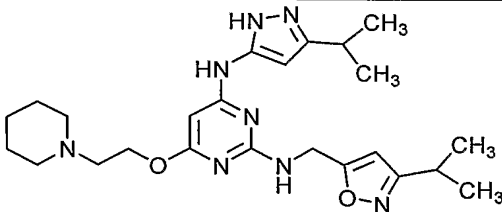
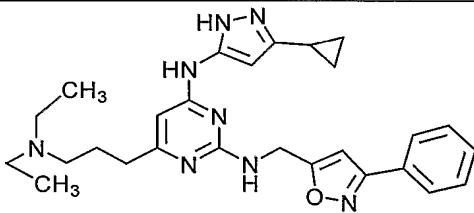
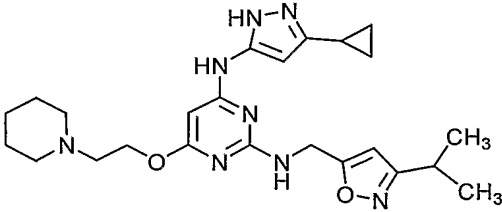
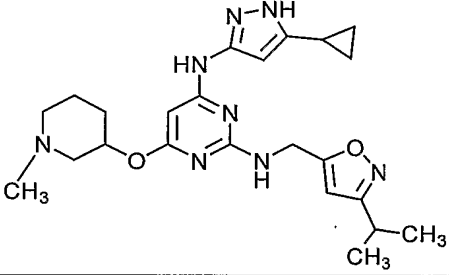
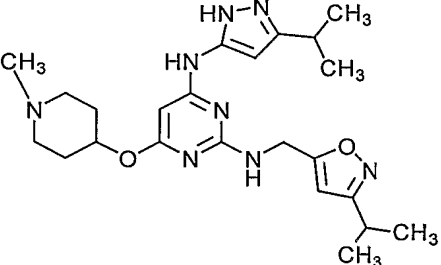
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|-----|---|---|
| 573 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^6 -[3-(diethylamino)propyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |
| 574 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^6 -[2-(diethylamino)ethyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |
| 575 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine |
| 576 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 577 |  | N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

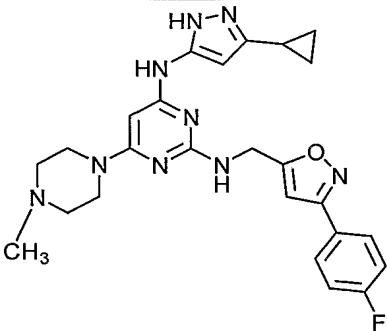
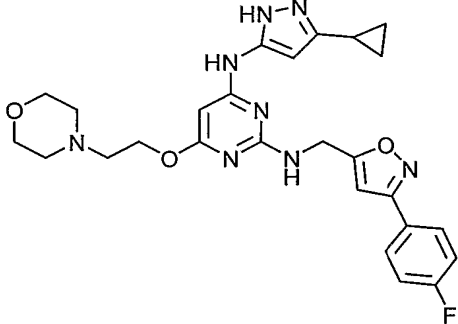
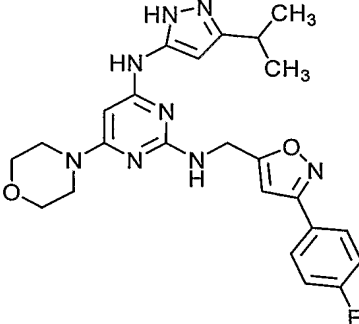
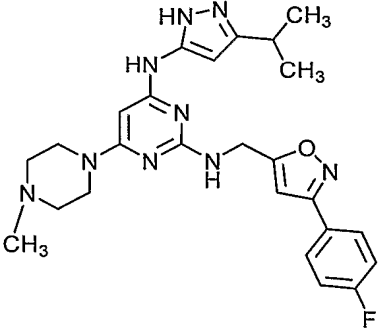
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| 578 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 579 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 580 |  | N^4 -[2-(diethylamino)ethyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4,6-triamine |
| 581 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4-diamine |
| 582 |  | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 583 |  | N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}- N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine |

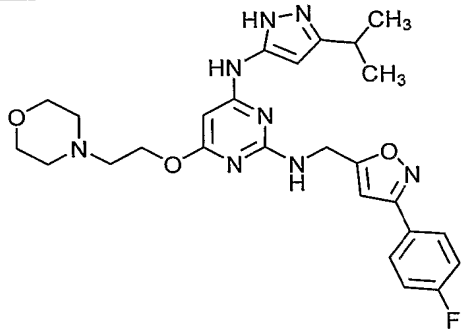
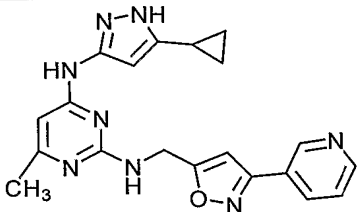
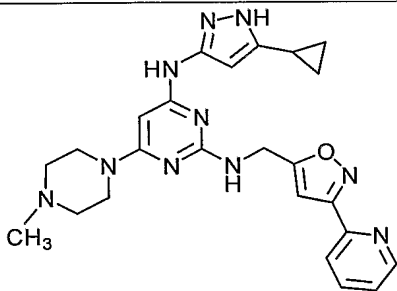
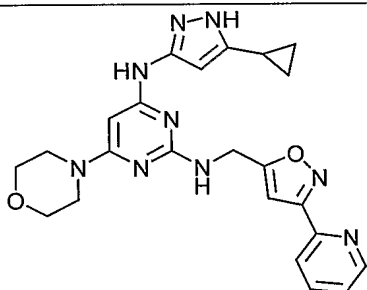
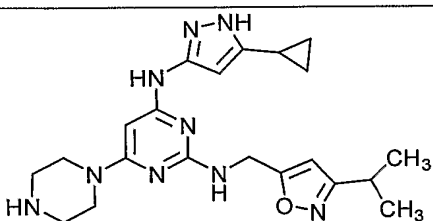
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| 584 |  | N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-2-[[3-phenylisoxazol-5-yl)methyl]oxy}pyrimidin-4-amine |
| 585 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(4-phenyl-1H-imidazol-2-yl)methyl]pyrimidine-2,4-diamine |
| 586 |  | 6-{[2-(dimethylamino)ethyl]oxy}-N ² -{[3-(1-methylethyl)isoxazol-5-yl)methyl]-N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4-diamine |
| 587 |  | N ² -{[3-(1-methylethyl)isoxazol-5-yl)methyl]-N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 588 |  | N ⁴ -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

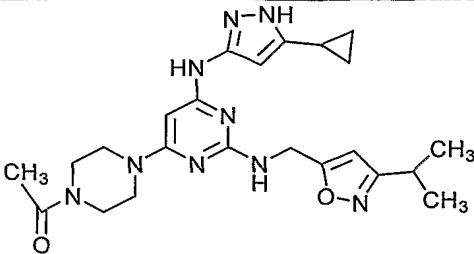
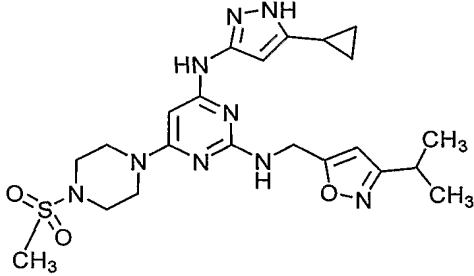
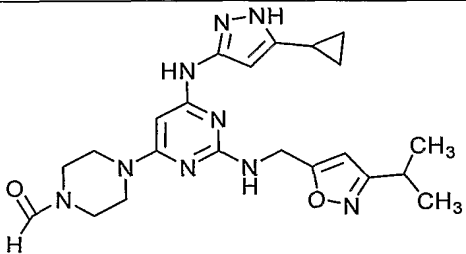
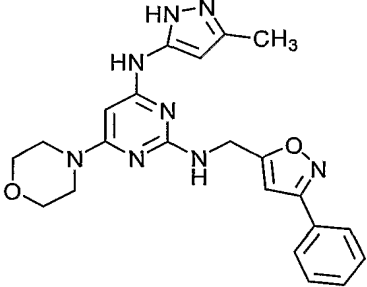
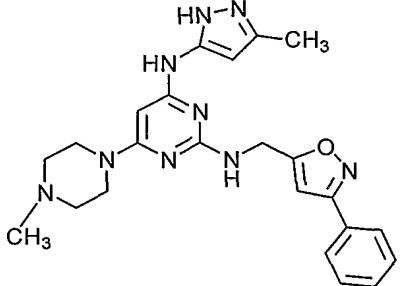
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| 589 |  | N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 590 |  | N^4 -[3-(diethylamino)propyl]- N^2 -{[3-(1-methylethyl)isoxazol-5-yl)methyl]- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4,6-triamine |
| 591 |  | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(3S)-3-methylpiperazin-1-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 592 |  | N^4 -[2-(diethylamino)ethyl]- N^6 -[5-(1-methylethyl)-1H-pyrazol-3-yl]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 593 |  | N^4 -[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-4-yl)oxy]- N^2 -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

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| 594 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 595 |  | N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 596 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-[3-(diethylamino)propyl]-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 597 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 598 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine |
| 599 |  | N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N ⁴ -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpiperidin-4-yl)oxy]pyrimidine-2,4-diamine |

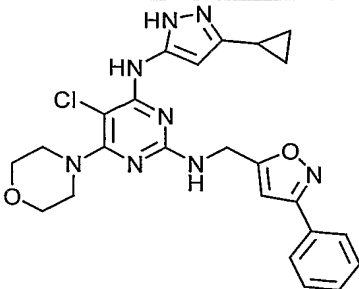
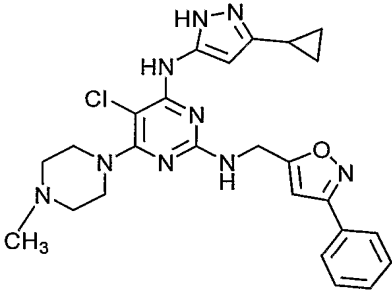
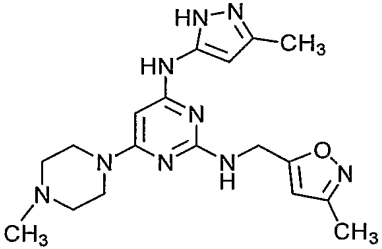
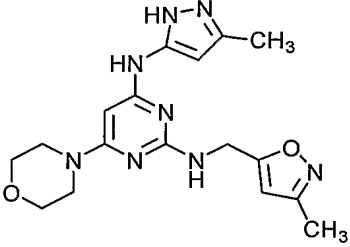
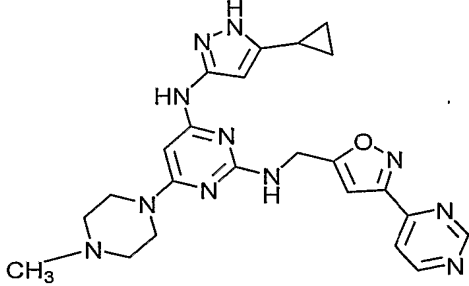
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| 600 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 601 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 602 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 603 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-4-yl)oxy]pyrimidine-2,4-diamine |
| 604 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-morpholin-4-ylpyrimidine-2,4-diamine |

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| 605 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 606 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)- N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 607 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 608 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |

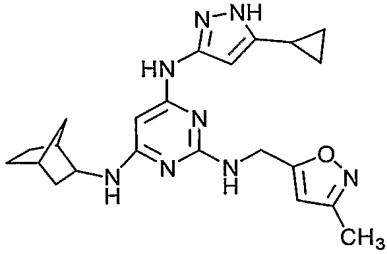
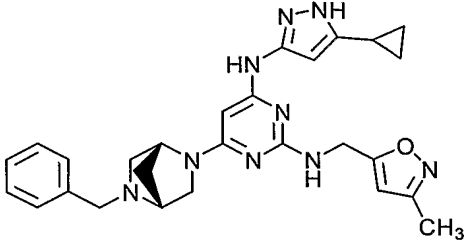
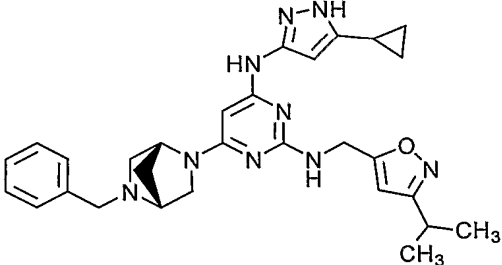
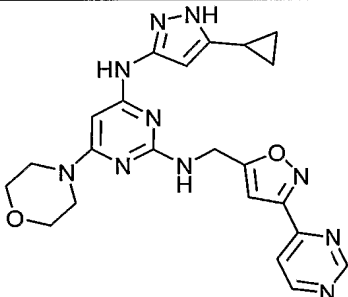
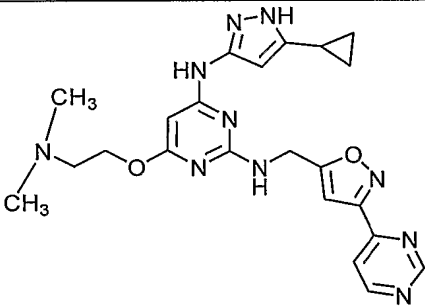
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| 609 |  | N^2 -{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}- N^4 -[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine |
| 610 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl- N^2 -[(3-pyridin-3-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 611 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 612 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-morpholin-4-yl- N^2 -[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 613 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-piperazin-1-ylpyrimidine-2,4-diamine |

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|-----|---|---|
| 614 |  | 6-(4-acetylpiperazin-1-yl)-N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 615 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[4-(methylsulfonyl)piperazin-1-yl]pyrimidine-2,4-diamine |
| 616 |  | 4-{6-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-([3-(1-methylethyl)isoxazol-5-yl]methyl)amino}pyrimidin-4-yl}piperazine-1-carbaldehyde |
| 617 |  | N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-morpholin-4-yl-N ² -{[3-(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine} |
| 618 |  | 6-(4-methylpiperazin-1-yl)-N ⁴ -(3-methyl-1H-pyrazol-5-yl)-N ² -{[3-(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine} |

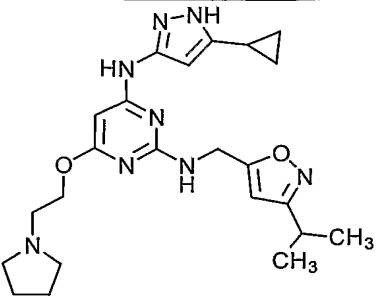
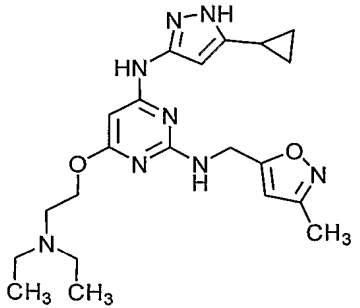
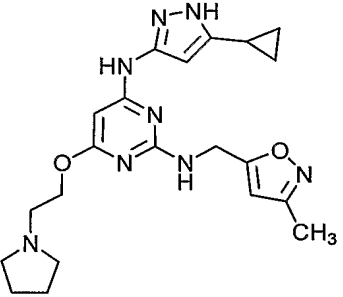
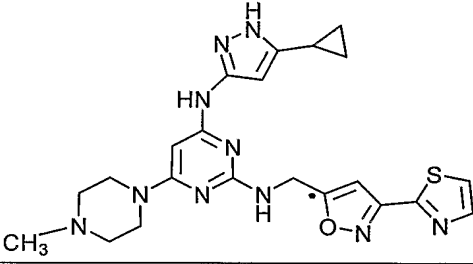
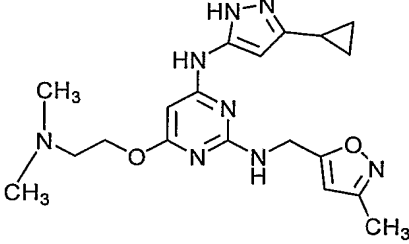
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| 619 | | N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-[(2-morpholin-4-ylethyl)oxy]-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 620 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(3-pyridin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 621 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(3,4-difluorophenyl)isoxazol-5-yl)methyl]}-6-methylpyrimidine-2,4-diamine |
| 622 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(2,4-difluorophenyl)isoxazol-5-yl)methyl]}-6-methylpyrimidine-2,4-diamine |
| 623 | | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N ² -[(3-pyrazin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

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| 624 |  | 5-chloro-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-morpholin-4-yl-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 625 |  | 5-chloro-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)-N ² -[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 626 |  | N ² -[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)-N ⁴ -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |
| 627 |  | N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 628 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N ² -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

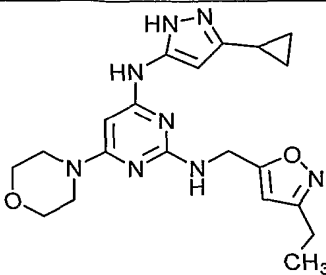
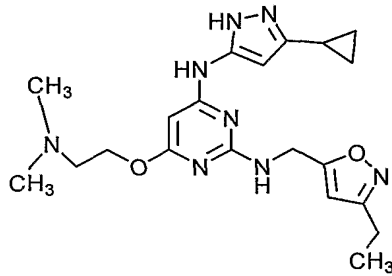
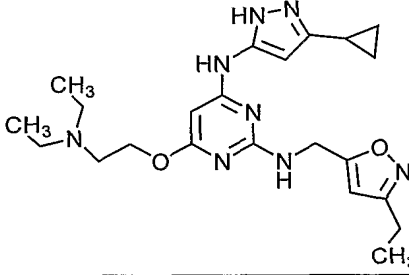
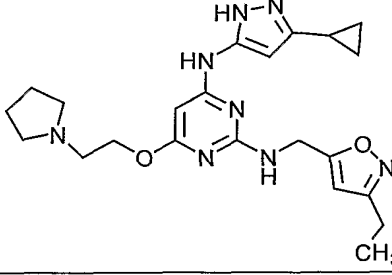
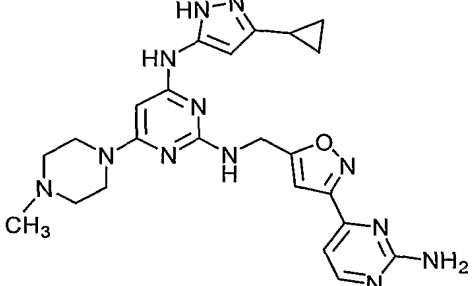
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| 629 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -[(3-furan-3-ylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |
| 630 | Chiral | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^6 -(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 631 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 632 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 633 | | N^4 -bicyclo[2.2.1]hept-2-yl- N^6 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine |

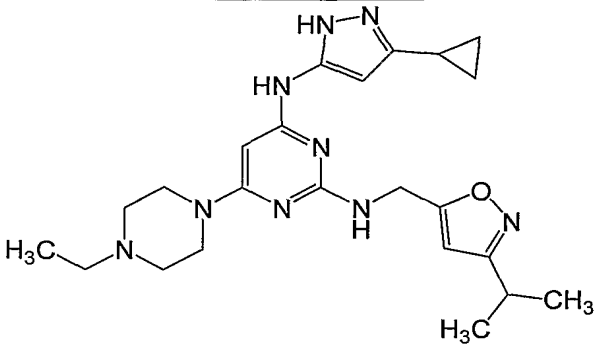
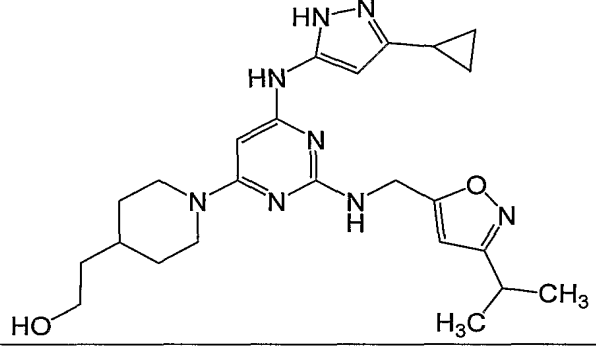
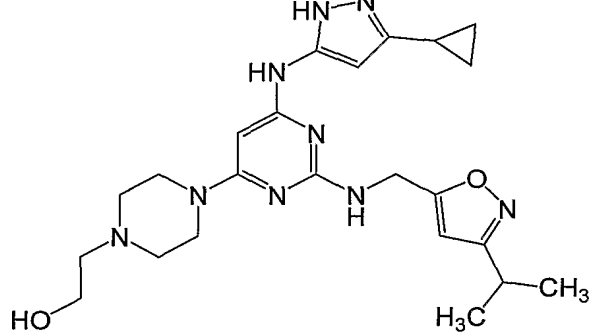
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| 634 |  | N ⁴ -bicyclo[2.2.1]hept-2-yl-N ⁶ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine |
| 635 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -[(3-methylisoxazol-5-yl)methyl]-6-[(1R,4R)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine |
| 636 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-N ² -{[3-(1-methylethyl)isoxazol-5-yl)methyl]-6-[(1R,4R)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine |
| 637 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-morpholin-4-yl-N ² -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 638 |  | N ⁴ -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N ² -[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

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| 639 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(5-fluoropyridin-2-yl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine |
| 640 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -{[3-(2-thienyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 641 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}- N^2 -[(3-pyridin-2-yl)isoxazol-5-yl]methylpyrimidine-2,4-diamine |
| 642 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)- N^2 -[(3-pyrimidin-5-yl)isoxazol-5-yl]methylpyrimidine-2,4-diamine |
| 643 | | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-morpholin-4-yl- N^2 -[(3-pyrimidin-5-yl)isoxazol-5-yl]methylpyrimidine-2,4-diamine |
| 644 | | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(diethylamino)ethyl]oxy}- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |

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|-----|---|---|
| 645 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[2-(2-methylisoxazol-5-yl)methyl]oxy]pyrimidine-2,4-diamine |
| 646 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-{[2-(diethylamino)ethyl]oxy}- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 647 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)- N^2 -[(3-methylisoxazol-5-yl)methyl]-6-[2-(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 648 |  | N^4 -(5-cyclopropyl-1H-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)- N^2 -{[3-(1,3-thiazol-2-yl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 649 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-[2-(dimethylamino)ethoxy]- N^2 -[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |

| | | |
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| 650 | | 6-{[2-(dimethylamino)ethyl]oxy}-N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |
| 651 | | 6-{[2-(diethylamino)ethyl]oxy}-N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine |
| 652 | | N ² -[(3-methylisoxazol-5-yl)methyl]-N ⁴ -(3-methyl-1H-pyrazol-5-yl)-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 653 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl-N ² -[2-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine |
| 654 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl-N ² -[1-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine |
| 655 | | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |

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| 656 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine |
| 657 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N ² -[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 658 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-{[2-(diethylamino)ethyl]oxy}-N ² -[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine |
| 659 |  | N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-N ² -[(3-ethylisoxazol-5-yl)methyl]-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine |
| 660 |  | N ² -{[3-(2-aminopyrimidin-4-yl)isoxazol-5-yl]methyl}-N ⁴ -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine |

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| 661 |  | N^4 -(3-cyclopropyl-1H-pyrazol-5-yl)-6-(4-ethylpiperazin-1-yl)- N^2 -{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine |
| 662 |  | 2-(1-{6-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperidin-4-yl)ethanol |
| 663 |  | 2-(4-{6-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperazin-1-yl)ethanol |

77. A metabolite of the compound according to claim 1.
78. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, excipient, or diluent.
79. A method of modulating the *in vivo* activity of IGF1R, the method comprising administering to a subject an effective IGF1R-modulating amount of a pharmaceutical composition according to claim 78.
80. A method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities effect directly or indirectly by IGF1R, the method

comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 78.

81. The method of claim 80 wherein the mammal is a human.
82. A method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of a compound according to claim 1 to a cell or a plurality of cells.
83. A method of inhibiting wild-type Abl in a cell, the method comprising administering an effective amount of a compound according to claim 1 to a cell or a plurality of cells.
84. The method of claim 83 wherein the wild-type Abl is T315I mutant.
85. A method of treating diseases or disorders in a mammal having a mutant-Abl malignancy, the method comprising administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 78.
86. The method of claim 85 wherein the mammal is a human.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
13 July 2006 (13.07.2006)

PCT

(10) International Publication Number
WO 2006/074057 A3

(51) International Patent Classification:

C07D 403/14 (2006.01) **A61K 31/42** (2006.01)
C07D 401/12 (2006.01) **A61P 35/00** (2006.01)
C07D 413/14 (2006.01) **A61P 29/00** (2006.01)
A61K 31/495 (2006.01)

(21) International Application Number:

PCT/US2005/047402

(22) International Filing Date:

28 December 2005 (28.12.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/640,439 30 December 2004 (30.12.2004) US
 60/704,863 1 August 2005 (01.08.2005) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

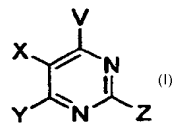
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

[Continued on next page]

(54) Title: PYRIMIDINE DERIVATIVES AS KINASE MODULATORS AND METHOD OF USE



(57) Abstract: The invention provides compounds and methods for inhibition of kinases, more specifically IGF 1 R kinases. The invention also provides compounds and methods for inhibition of wildtype Abl. The invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Compounds of the invention inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in

cellular activities as mentioned above, and the invention includes compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions. A compound of formula (I), or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein, V is NR₁R_{1a}, or O-R₁, wherein X is H, halo, C₁-C₆ alkyl, NO₂, mono-, di-, or tri-halo substituted methyl, NR₁₃R₁₄, C(O)O-C₁-C₆ alkyl, or N(R₁₃)-C(O)-C₁-C₆ alkyl; Y is H, halo, OH, C₁-C₆ alkyl, C₀-C₆alkyl-NR₁₅R₁₆, NR₁₅R₁₆, C₁-C₆ alkoxy, -N(R₁₃)-(CH₂)_n-NR₁₅R₁₆, -C(O)O-C₁-C₆ alkyl, -O-(CH₂)_n-NR₁₅R₁₆, -C(O)-C₁-C₆ alkyl, -C₀-C₆-alkyl-R₂₁, -O-R₂₁, -C(O)-R₂₁, -O-(CH₂)_n-R₂₁, -C(O)-NR₁₃R₁₄, -C(O)-N(R₁₃)-aryl, -C(O)-N(R₁₃)(CH₂)_n-NR₁₅R₁₆, -C(O)-N(R₁₃)-(CH₂)_n-aryl -C(O)-N(R₁₃)-(CH₂)_n-heterocyclyl; or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S. Z is H, NR₂R₃, -S-R_{2a}, or -O-R_{2a}



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(88) Date of publication of the international search report:

26 October 2006

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/047402

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/14 C07D401/12 C07D413/14 A61K31/495 A61K31/42
A61P35/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

13 July 2006

Date of mailing of the international search report

14/08/2006

Name and mailing address of the ISA/
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/047402

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

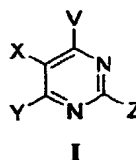
International application No.

PCT/US2005/047402

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The invention provides compounds and methods for inhibition of kinases, more specifically IGF1R kinases. The invention also provides compounds and methods for inhibition of wild-type Abl. The invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Compounds of the invention inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, and the invention includes compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

A compound of Formula I,



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

V is NR_1R_{1a} , or $\text{O}-\text{R}_1$, wherein

X is H, halo, $\text{C}_1\text{-C}_6$ alkyl, NO_2 , mono-, di-, or tri-halo substituted methyl, $\text{NR}_{13}\text{R}_{14}$, $\text{C}(\text{O})\text{O}-\text{C}_1\text{-C}_6$ alkyl, or $\text{N}(\text{R}_{13})-\text{C}(\text{O})-\text{C}_1\text{-C}_6$ alkyl;

Y is H, halo, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_6$ alkyl- $\text{NR}_{15}\text{R}_{16}$, $\text{NR}_{15}\text{R}_{16}$, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})\text{O}-\text{C}_1\text{-C}_6$ alkyl, $-\text{O}-(\text{CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{C}_1\text{-C}_6$ alkyl, $-\text{C}_0\text{-C}_6\text{-alkyl-R}_{21}$, $-\text{O-R}_{21}$, $-\text{C}(\text{O})-\text{R}_{21}$, $-\text{O}-(\text{CH}_2)_n\text{-R}_{21}$, $-\text{C}(\text{O})-\text{NR}_{13}\text{R}_{14}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})\text{-aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-NR}_{15}\text{R}_{16}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-aryl}$, $-\text{C}(\text{O})-\text{N}(\text{R}_{13})-(\text{CH}_2)_n\text{-heterocyclyl}$;

or X and Y together with the atoms to which they are attached form a 4-7 membered heterocyclyl or heteroaryl group containing one or two heteroatoms independently selected from O, N, and S

Z is H, NR_2R_3 , $-\text{S-R}_{2a}$, or $-\text{O-R}_{2a}$.